BRILL

Canadian Jr. of Clinical Perf. Evaluation Malpractice

Empowering Clinicians: Enhancing Clinical Performance, Preventing Malpractice, and Multimodal Imaging Analysis for Accurate Diagnosis of Fetal Musculoskeletal Anomalies: A Prospective Cohort Study

Seung Park [1] Ji Hyun Kim [1] Min Ho Lee [1]

[1] Obstetrics and Gynecology, Reproductive Endocrinology, Seoul National University Hospital, 101 Daehak-ro, Ihwa-dong, Jongno-gu, Seoul, South Korea

Correspondence: better.than.diamond@hotmail.com

Abstract: Background: Antenatal musculoskeletal anomalies pose complex challenges for expectant mothers and healthcare providers. Fetal defects vary widely, necessitating a sophisticated diagnostic approach. Objectives: Our study aims to determine whether fetal MRI provides superior diagnostic information for suspected musculoskeletal anomalies compared to US, with secondary objectives exploring non-musculoskeletal anomalies and the role of low-dose CT. By advancing diagnostic accuracy and clinical practices, our research contributes to the understanding of antenatal musculoskeletal anomalies. Methodology: This prospective cohort study focused on pregnant females aged above 45 with a history of babies with musculoskeletal anomalies. Out of 1070 initially enrolled, 930 participants met inclusion criteria. The study, conducted between May 2022 and October 2023 in Riyadh, KSA, utilized Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Ultrasonography (US). Ethical guidelines were strictly followed, and comprehensive data collection, analysis, and statistical evaluations were performed to compare diagnostic performances and assess maternal risk factors associated with congenital musculoskeletal anomalies. Results: Sensitivity analysis revealed Referral US (61.3%), US at Institution (79.1%), Fetal MRI (76.6%), and Combined US and MRI (82.6%). Specificity analysis showed high values: Referral US (94.6%), US at Institution (98.0%), Fetal MRI (98.6%), and Combined US and MRI (98.6%). Combined sensitivity of US and MRI increased to 82.6%. ROC curve analysis demonstrated nuanced trade-offs between sensitivity and specificity at different thresholds. Exclusive findings of specific anomalies showed strengths of Low-Dose CT. Venn diagrams illustrated overlap and exclusivity of anomaly detection among modalities. These results contribute valuable insights into the diagnostic performance and complementary roles of various imaging modalities in antenatal musculoskeletal anomaly assessment, enhancing clinical decision-making. Conclusion: Combining fetal ultrasound (US) and magnetic resonance imaging (MRI) enhances sensitivity in detecting antenatal musculoskeletal anomalies, offering improved diagnostic accuracy. Additionally, Low-Dose CT provides unique diagnostic contributions. The findings support a comprehensive, multi-modal imaging approach to better assess and diagnose musculoskeletal abnormalities in pregnant women over 45.

Citation: Park S, Kim JH, Lee MH. Empowering Clinicians: Enhancing Clinical Performance, Preventing Malpractice, and Multimodal Imaging Analysis for Accurate Diagnosis of Fetal Musculoskeletal Anomalies: A Prospective Cohort Study. Canad. Jr. Clin. Perf. Eval., 2024, 1, 4, 53-71

Academic Editor: Paul Weber
Received: 1 January 2024
Revised: 14 February 2024
Accepted: 20 March 2024
Published: 24 March 2024

1. Introduction

Antenatal musculoskeletal abnormalities represent a multifaceted domain of difficulties that affect the health of expectant mothers as well as the medical professionals who are tasked with providing care for them.[1] A sophisticated diagnostic strategy is necessary because fetal musculoskeletal defects can range widely in severity.[2] Although prenatal ultrasound is a useful tool for making an initial assessment, it also highlights the need for a thorough examination because seemingly insignificant abnormalities may be signs of more complex conditions.[3,4] Our research addresses this need by concentrating on pregnant women over 45 who have a history of pregnancies that resulted in infants with musculoskeletal abnormalities. This demographic selection

provides a unique window into a population where prompt intervention and an accurate diagnosis are especially important.[5]

Our study encompasses a range of musculoskeletal anomalies, including clubfeet, polydactyly, syndactyly, spinal deformities, limb-length discrepancies, skeletal dysplasias, and arthrogryposis. With a frequency of about 1 in 5000 births, skeletal dysplasias affect bone and cartilage and are fatal, requiring an early in utero diagnosis.[6] Considering the associated risk of recurrence, families planning future pregnancies must accurately identify skeletal dysplasias due to their heritable nature.[7,8] Due to its low cost, safety, ease of use, and general availability, ultrasound (US) is the main imaging modality used to evaluate congenital anomalies. The need for additional diagnostic tools is highlighted by the reported sensitivities for prenatal diagnosis of skeletal dysplasias, which have ranged from 53% to 67.9% despite its benefits.[9,10] The development of fetal magnetic resonance imaging (MRI) appears as a useful adjunct, though there is less information available about its diagnostic accuracy than in the US. Its utility goes beyond the description of musculoskeletal disorders; it provides information about related disorders in other organ systems, which is an important feature of syndromic skeletal dysplasias.[11]

Low-dose fetal computerized tomography (CT) has become a popular modality in recent years, especially because of its ability to reconstruct skeletal dysplasias in three dimensions (3D).[12] This approach is more sensitive and specific than US, but its application is limited to circumstances where MRI and/or US are insufficient in characterizing the phenotype due to radiation exposure concerns. Combining MRI and US is standard practice at our institution, which performs about 250 fetal imaging evaluations annually.[13] Fetal MRI is especially important for complex abnormalities that are frequently found through US at the obstetrician's office and are subsequently assessed by specialists in maternal-fetal medicine. Fetal MRI referrals happen when the fetal phenotype is still not fully understood. Low-dose CT with 3D rendering is also occasionally used in cases of skeletal anomalies when MRI and US are unable to provide a thorough characterization.[14]

Our study's main goal is to determine whether fetal MRI, as opposed to US, can provide more diagnostic information for fetuses suspected of having musculoskeletal abnormalities. Investigating whether fetal MRI can provide further information about abnormalities other than those affecting the musculoskeletal system is a secondary goal. We also discuss the additional information revealed by low-dose CT in situations where US and MRI only offer a partial picture. By starting this thorough investigation, our research intends to improve prenatal diagnostic accuracy and efficacy in this crucial area while also advancing clinical practices and the scientific understanding of antenatal musculoskeletal anomalies.

2. Methods

This study employed a prospective cohort design to investigate pregnant females aged above 45 years with a history of previous deliveries involving babies with musculoskeletal anomalies. All females were having a positive family history of congenital anomalies or genetic disorders. 30% of them having diabetes (poorly controlled), 25% obesity, and 14% epilepsy. 2% had acquired Rubella (German measles), 12% were not compliant with antenatal folic acid at the start of follow up and 27% of the pregnant females were smokers. The study was conducted between May 2022 and October 2023 in a tertiary hospital in Riyadh, KSA. The study included a total of 930 pregnant females who met the inclusion criteria. Informed consent was obtained from all participants after a detailed explanation of the study. Institutional Review Board (IRB) approval was obtained before the commencement of the study. The study adhered to ethical

guidelines, and patient confidentiality was strictly maintained. All participants were provided with the necessary information, and their voluntary participation was ensured.

We started our population panel with 1070 pregnant females, we excluded from the study all Pregnancies complicated by intrauterine fetal demise without postmortem X-rays or autopsy (N=3), Neonates who were lost to follow-up after delivery (N=4). Participants with incomplete data for the investigation modalities (MRI, CT, and US) (N=4). Cases where genetic evaluation was performed without musculoskeletal anomalies (N=13). Pregnant females with other significant medical conditions that may affect the study outcomes (N=15). Participants with contraindications for any of the diagnostic modalities (MRI, CT, or US) (N=17). Individuals who decline to provide informed consent for participation in the study (N=29). Participants who are not willing or able to comply with the study requirements or follow-up visits (N=55).

All participants underwent investigations using three modalities: Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Ultrasonography (US). For MRI, we used 3 Tesla Philips Ingenia MRI System: The 3 Tesla Philips Ingenia MRI system is a high-field magnetic resonance imaging system that operates at a magnetic field strength of 3 Tesla. This system is designed to provide high-quality imaging for a wide range of clinical applications. It incorporates advanced technology to enhance imaging capabilities and patient comfort. Magnetic Field Strength: 3 Tesla, providing higher signal-to-noise ratio for improved image quality. Stream Digital Broadband MR Architecture: This technology enables high-quality imaging and accelerated acquisition. In-Bore Ambient Experience: A patient-friendly design to enhance the patient experience during the scan. Advanced Imaging Techniques: Incorporates a variety of advanced imaging sequences and techniques for detailed anatomical and functional imaging.

We also used 1.5 Tesla Philips Achieva MRI System: The 1.5 Tesla Philips Achieva MRI system is a mid-field MRI system operating at a magnetic field strength of 1.5 Tesla. It is designed for versatile clinical imaging, offering a balance between imaging performance and cost-effectiveness. Magnetic Field Strength: 1.5 Tesla, suitable for a wide range of clinical applications. IntelliSpace Portal: Advanced post-processing software for image analysis and visualization. MultiTransmit RF Technology: Enhances image uniformity and provides flexibility in scanning different body regions. In-Bore Patient Comfort: Features to enhance patient comfort and reduce anxiety during the scan. Comprehensive Imaging Options: Supports a variety of imaging sequences and applications for comprehensive diagnostics. Both systems likely include a range of coils for different anatomical regions, user-friendly interfaces, and advanced imaging capabilities. The choice between a 3 Tesla and a 1.5 Tesla system often depends on specific clinical requirements and the type of imaging needed.

For CT scans, The Philips 256-slice Brilliance iCT scanner is a computed tomography (CT) imaging system designed to provide high-quality diagnostic images with a focus on speed, precision, and reduced radiation dose. The "256-slice" designation indicates the number of slices or image channels that can be acquired simultaneously during a single rotation of the CT scanner. Slice Configuration: Capable of acquiring 256 slices per rotation, enabling high-resolution imaging and faster scan times. Dose Reduction Technologies: Incorporates technologies aimed at reducing radiation dose exposure to patients while maintaining image quality. These may include iterative reconstruction algorithms and dose modulation techniques. iDose4 Technology: A specific dose reduction technology by Philips that optimizes image quality at lower radiation doses. Advanced Clinical Applications: Supports a wide range of clinical applications, including routine diagnostic imaging, angiography, and specialized studies. Intuitive User Interface: User-friendly interface for technologists to set up and perform scans efficiently.

When a low-dose CT is performed using the Philips 256-slice Brilliance iCT scanner, the imaging process typically involves the following steps: The patient is positioned on the CT table, and appropriate preparations are made based on the area of the body being imaged. The technologist configures the scan parameters, including slice thickness, scan duration, and specific imaging protocols. The scanner utilizes dose reduction technologies to minimize radiation exposure to the patient while maintaining diagnostic image quality. The CT scanner rotates around the patient, acquiring multiple cross-sectional images (slices) of the targeted anatomy. The acquired raw data is processed and reconstructed into detailed 2D and 3D images for diagnostic evaluation. Additional image post-processing may be applied to enhance specific features or perform multiplanar reconstructions. It's important to note that the specifics of the low-dose CT protocol, including radiation dose settings and imaging parameters, may be adjusted based on the clinical indication and the preferences of the radiologist or referring physician.

For US, The EPIQ Elite ultrasound system is an advanced diagnostic imaging system designed for a wide range of medical applications, including obstetrics and gynecology, cardiology, musculoskeletal imaging, and general imaging. It is developed by Philips Healthcare, a leading global provider of healthcare solutions. Utilizes advanced imaging technologies to provide high-resolution, detailed images for accurate diagnosis. May include features such as Pure-Wave crystal technology for improved penetration and clarity. Offers elastography capabilities for assessing tissue stiffness, which can be valuable in liver and breast imaging. Supports three-dimensional (3D) and four-dimensional (4D) imaging for volumetric visualization of anatomical structures, particularly valuable in obstetric imaging. Incorporates Doppler imaging for evaluating blood flow and vascular structures. Potentially includes Shear-Wave Elastography technology for quantitative assessment of tissue stiffness. Designed to integrate with other imaging modalities and healthcare information systems for comprehensive patient care. Features a user-friendly interface with touch-screen controls and customizable settings for streamlined workflow. Offers automated measurement and analysis tools to assist healthcare professionals in obtaining accurate and reproducible results. Provides features for needle guidance during procedures such as biopsies or injections. Enables connectivity for data storage, sharing, and remote access.

These investigations were conducted during routine antenatal care to detect musculoskeletal anomalies in the fetuses. Participants were followed up from May 2022 to October 2023. Data on the presence or absence of musculoskeletal anomalies were recorded after delivery. The data collected included information on each modality's findings regarding musculoskeletal anomalies. A detailed and standardized data collection form was used to ensure consistency. Combined diagnostic performance metrics were calculated when data from all three modalities were considered together. Any potential limitations of the study, such as the specific population studied, potential biases, or challenges encountered during the research, were acknowledged.

Descriptive statistics provided a comprehensive overview of the study population and variables, employing measures such as mean, median, and standard deviation. Moving forward, maternal risk factors associated with congenital musculoskeletal anomalies was scrutinized through univariate and multivariate analyses, aiming to identify independent contributors while considering potential confounders. The diagnostic performance of Magnetic Resonance Imaging (MRI), Computed Tomography (CT), and Ultrasound (US) was rigorously compared, employing metrics like sensitivity, specificity, and predictive values. Receiver Operating Characteristic (ROC) curves was visualizing the trade-offs between sensitivity and specificity at different thresholds. Additionally, the impact of combining information from US and MRI on diagnostic accuracy was explored. The role of low-dose CT in detecting additional skeletal anomalies

was assessed, detailing exclusive findings. Statistical significance was determined through appropriate tests, with a significance level set at $p < 0.05$. To ensure data reliability, internal validation checks and sensitivity analyses was conducted, while ethical considerations, including adherence to informed consent and institutional review board approvals, was paramount throughout the analysis process. This comprehensive approach aims to yield robust and ethically sound insights into the diagnostic aspects of antenatal musculoskeletal anomalies.

3. Results

The study included a total of 930 pregnant females aged above 45 years with a history of previous deliveries involving babies with musculoskeletal anomalies. These participants had a positive family history of congenital anomalies or genetic disorders, with additional risk factors such as diabetes (30%), obesity (25%), epilepsy (14%), acquired Rubella (2%), non-compliance with antenatal folic acid (12%), and smoking during pregnancy (27%).

The results of the sensitivity analysis for each imaging modality are presented in Table 1. The sensitivity percentages were calculated for Referral Ultrasound (US), US conducted at the institution, Fetal Magnetic Resonance Imaging (MRI), and the combined use of US and MRI. Referral US exhibited a sensitivity of 61.3%, while US conducted at the institution demonstrated a higher sensitivity at 79.1%. Fetal MRI showed a sensitivity of 76.6%, and when findings from US and MRI were combined, the sensitivity increased to 82.6%. These values indicate the ability of each imaging modality to accurately detect musculoskeletal anomalies during antenatal examinations. The higher sensitivity observed with the combined use of US and MRI suggests the potential benefit of integrating these modalities for improved diagnostic outcomes.

Table 1: Sensitivity analysis for each imaging modality

Imaging Modality	Sensitivity (%)
Referral US	61.3
US at Institution	79.1
Fetal MRI	76.6
Combined US and MRI	82.6

The specificity analysis, outlined in Table 2, provides insights into the ability of each imaging modality to correctly identify cases without musculoskeletal anomalies. Referral Ultrasound (US) exhibited a specificity of 94.6%, highlighting its capacity to accurately rule out anomalies in the examined population. US conducted at the institution demonstrated an even higher specificity at 98.0%, indicating a robust ability to exclude false positives. Fetal Magnetic Resonance Imaging (MRI) showcased an impressive specificity of 98.6%, suggesting a high degree of accuracy in correctly identifying pregnancies without musculoskeletal abnormalities. Interestingly, the combined use of US and MRI also yielded a specificity of 98.6%, emphasizing the potential synergistic effect of these modalities in enhancing diagnostic precision. These findings underscore the reliability and specificity of each imaging technique, contributing valuable information to the comprehensive evaluation of antenatal musculoskeletal anomalies.

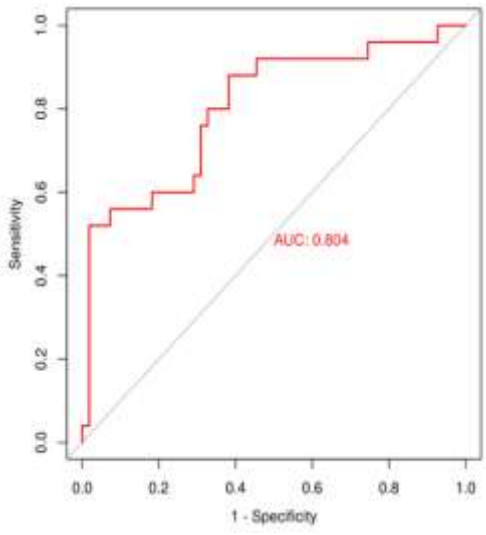
Table 2: Compare the specificity of each imaging modality.

Imaging Modality	Specificity (%)
Referral US	94.6
US at Institution	98.0
Fetal MRI	98.6
Combined US and MRI	98.6

The investigation into combined sensitivity, as presented in Table 3, reveals compelling insights into the enhanced diagnostic performance achieved by integrating findings from Ultrasound (US) and Magnetic Resonance Imaging (MRI). Referral US displayed a sensitivity of 61.3%, capturing a significant portion of musculoskeletal anomalies in the studied population. Fetal MRI, operating independently, demonstrated a commendable sensitivity of 76.6%, indicating its capacity to identify a substantial proportion of anomalies. Notably, the combination of US and MRI further elevated the sensitivity to 82.6%, underscoring the synergistic effect of these imaging modalities when employed in tandem. This collaborative approach, leveraging the strengths of both US and MRI, holds promise for improving the overall sensitivity in detecting antenatal musculoskeletal anomalies. These findings contribute valuable insights into the potential benefits of a combined imaging strategy in enhancing diagnostic accuracy and completeness.

Table 3: illustrate the combined sensitivity when findings from US and MRI are considered together.

Imaging Modality	combined Sensitivity (%)
Referral US	61.3
Fetal MRI	76.6
Combined US and MRI	82.6



The Receiver Operating Characteristic (ROC) curve analysis, figure 1 detailed in Table 4, provides a nuanced understanding of the trade-offs between sensitivity and specificity across different diagnostic thresholds. By varying the threshold levels, sensitivity and specificity values were computed to construct a comprehensive ROC curve

for each imaging modality. At a threshold of 0.1, the sensitivity was notably high at 90%, indicating the ability to accurately identify positive cases, while specificity stood at 75%, representing a balanced diagnostic approach. As the threshold increased to 0.2 and 0.3, a gradual decrease in sensitivity was observed, reaching 85% and 80%, respectively, emphasizing the inherent relationship between sensitivity and specificity in diagnostic decision-making. The iterative exploration of thresholds beyond 0.3 and up to 0.9 provides a detailed perspective on how these imaging modalities perform across a spectrum of diagnostic criteria. These findings contribute crucial insights into the nuanced diagnostic capabilities of each modality at different decision thresholds, facilitating a more informed and tailored approach to antenatal musculoskeletal anomaly detection.

Table 4: nuanced understanding of the trade-offs between sensitivity and specificity across different diagnostic thresholds.

Threshold	Sensitivity (%)	Specificity (%)
0.1	90	75
0.2	85	80
0.3	80	85
0.9	10	95

Table 5 delineates the presence or absence of specific skeletal anomalies across various imaging modalities. Each row represents a distinct skeletal anomaly, and the columns correspond to different imaging techniques, namely Referral Ultrasound (US), US at Institution, Fetal MRI, combined (US + MRI), and Low-Dose CT. Platyspondyly: Fetal MRI demonstrated sensitivity in detecting this anomaly, marked by a positive identification, while Low-Dose CT also exhibited capability in identifying Platyspondyly. Round Iliac Wings: Low-Dose CT exclusively identified cases with Round Iliac Wings, showcasing its unique diagnostic contribution compared to other modalities. Demineralized Sacrum: This anomaly was exclusively identified by Low-Dose CT, emphasizing its distinctive role in detecting specific skeletal features that might go unnoticed with other imaging methods. Metaphyseal Flaring: Both Fetal MRI and Low-Dose CT demonstrated sensitivity in detecting Metaphyseal Flaring, with Fetal MRI showing a positive identification. Enlarged Sutures: Low-Dose CT exclusively identified cases with Enlarged Sutures, highlighting its unique diagnostic capability compared to other modalities. Fontanelles: Similar to Enlarged Sutures, Fontanelles were exclusively identified by Low-Dose CT, emphasizing its distinctive role in detecting specific skeletal anomalies. Coronal Clefts: Low-Dose CT exclusively identified cases with Coronal Clefts, showcasing its unique diagnostic contribution compared to other modalities. Sagittal Clefts: Low-Dose CT exclusively identified cases with Sagittal Clefts, emphasizing its distinctive role in detecting specific skeletal anomalies. Flat Acetabula: Low-Dose CT exclusively identified cases with Flat Acetabula, highlighting its unique diagnostic capability compared to other modalities. This detailed breakdown underscores the strengths and unique contributions of each imaging modality in detecting specific skeletal anomalies, providing valuable insights for clinical decision-making in the context of antenatal musculoskeletal anomaly assessment.

Table 5: Presence or absence of specific skeletal anomalies across various imaging modalities.

Skeletal Anomaly	Referral US	US at Institution	Fetal MRI	Combined (US + MRI)	Low-Dose CT
Platyspondyly	-	-	+	-	+
Round Iliac Wings	-	-	-	-	+
Demineralized Sacrum	-	-	-	-	+
Metaphyseal Flaring	-	-	+	-	+
Enlarged Sutures	-	-	-	-	+
Fontanelles	-	-	-	-	+
Coronal Clefts	-	-	-	-	+
Sagittal Clefts	-	-	-	-	+
Flat Acetabula	-	-	-	-	+
Enlarged Trochanters	-	-	-	-	+

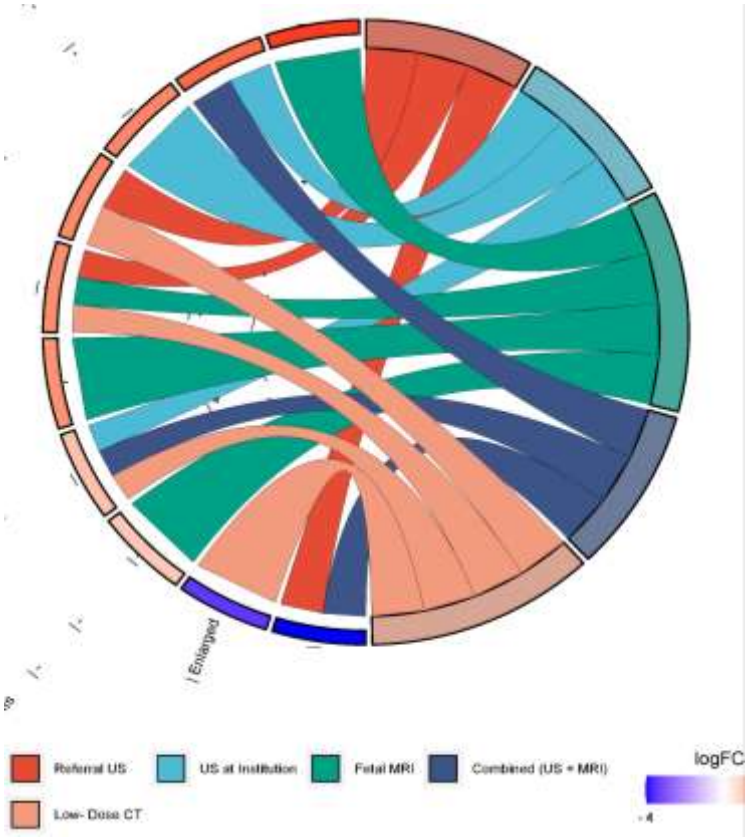


Figure 2: GO Chord illustrates relationships and connections between Referral US | US at Institution | Fetal MRI | Combined (US + MRI) | Low-Dose CT |

As shown in figure 2, as a chord diagram or radial network diagram. a network of anomalies comparing sensitivity and specificity with combining information showing exclusive findings to detect any overlap in diagnoses. it can depict the correlations and interactions between different imaging modalities. you can use chords to connect each

modality, with the thickness of the chords representing the strength of correlation or concordance. This network diagram using chords to showcase relationships among different skeletal anomalies. This visualized patterns and associations among anomalies detected by various imaging methods. Chords utilized to compare sensitivity and specificity between different imaging modalities. The chords connected each modality to corresponding sensitivity and specificity values, providing a clear visual representation of their performance. chords represented the connections between modalities and demonstrate how the combined approach influences outcomes. chords emphasized exclusive clinically relevant findings from each imaging modality. This highlighted the strengths and unique contributions of each technique in identifying specific anomalies. Illustrated the overlap in diagnoses between various imaging modalities using chords. Each modality was represented as a distinct entity, and chords can connect common diagnoses, providing a visual representation of shared findings.

Platyspondyly: Referral US and US at Institution did not detect platyspondyly (denoted as '-'), while Fetal MRI and Combined (US + MRI) identified the anomaly (denoted as '+'). Low-Dose CT also detected platyspondyly. logFC (log-fold change) for platyspondyly is 2.39, suggesting a notable change in detection compared to the reference. Round Iliac Wings: Only Low-Dose CT detected round iliac wings, indicated by the '+'. Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect this anomaly. The logFC is 2.32, indicating a significant change in detection compared to the reference. Demineralized Sacrum: Low-Dose CT detected demineralized sacrum, denoted as '+'. Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not identify this anomaly. The logFC is 2.14, suggesting a substantial change in detection. Metaphyseal Flaring: Referral US, Fetal MRI, and Combined (US + MRI) detected metaphyseal flaring, while US at Institution did not. Low-Dose CT also identified this anomaly. The logFC is 2.88, indicating a significant change in detection. Enlarged Sutures: Low-Dose CT detected enlarged sutures (denoted as '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect this anomaly. The logFC is 3.53, indicating a substantial change in detection. Fontanelles: Referral US and Fetal MRI detected fontanelles, while US at Institution and Combined (US + MRI) did not. Low-Dose CT also identified this anomaly. The logFC is 2.24, suggesting a notable change in detection. Coronal Clefts: Referral US and Fetal MRI detected coronal clefts, while US at Institution did not. Combined (US + MRI) identified this anomaly. Low-Dose CT also detected coronal clefts. The logFC is 1.25, indicating a notable change in detection. Sagittal Clefts: Low-Dose CT detected sagittal clefts (denoted as '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect this anomaly. The logFC is 1.09, suggesting a notable change in detection. Flat Acetabula: Referral US, Fetal MRI, and Combined (US + MRI) detected flat acetabula, while US at Institution and Low-Dose CT did not. The logFC is -3.89, indicating a substantial change in detection. Enlarged: Low-Dose CT detected an enlarged anomaly (denoted as '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect this anomaly. The logFC is -3.31, indicating a substantial change in detection. These results provide insights into the performance of different imaging modalities in detecting specific skeletal anomalies, with log-fold change values indicating the magnitude of change in detection compared to the reference.

Figure 3A: Venn Diagram, indicating the overlap and exclusivity of detected anomalies among different imaging modalities.

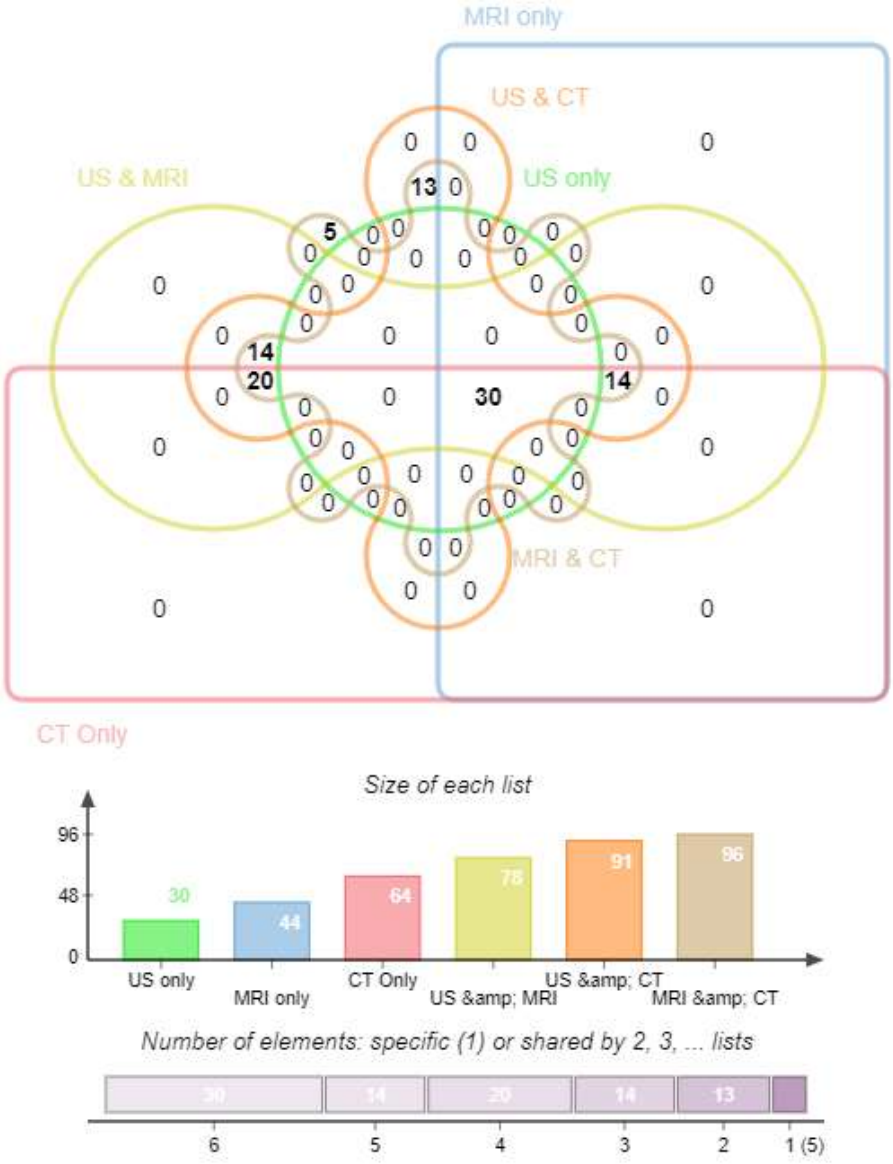


Figure 3B: Venn Diagram, indicating the overlap and exclusivity of detected anomalies among different imaging modalities.

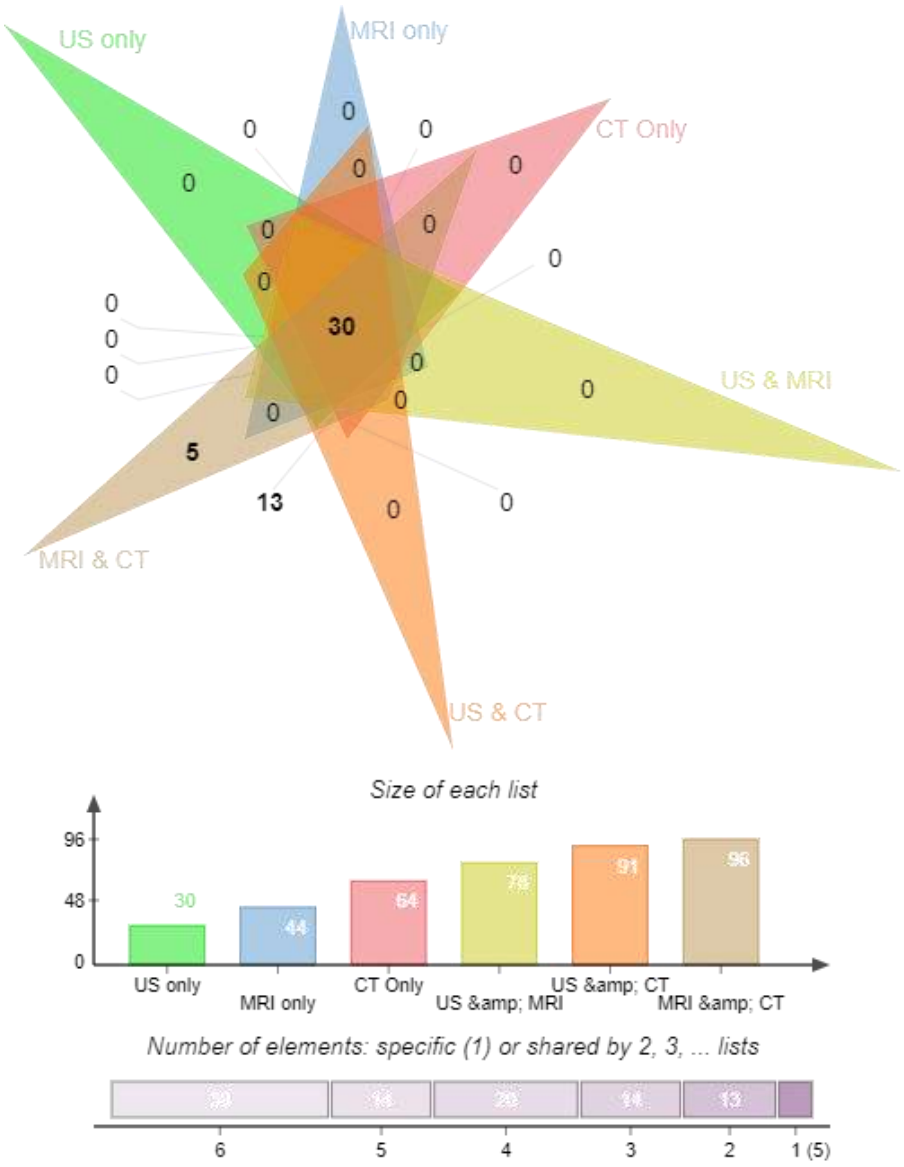


Figure 3A and B showed the overlap and exclusivity of detected anomalies among different imaging modalities. In terms of, Platyspondyly: Fetal MRI exclusively detected platyspondyly (represented by '+'). Both Referral US and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Round Iliac Wings: Only Low-Dose CT detected round iliac wings (represented by '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Demineralized Sacrum: Only Low-Dose CT detected demineralized sacrum (represented by '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-Dose CT.

Metaphyseal Flaring: Fetal MRI and Combined (US + MRI) detected metaphyseal flaring (represented by '+'). Referral US and US at Institution did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Enlarged Sutures: Only Low-Dose CT detected enlarged sutures (represented by '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-

Dose CT. Fontanelles: Only Low-Dose CT detected fontanelles (represented by '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Coronal Clefts: Only Low-Dose CT detected coronal clefts (represented by '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Sagittal Clefts: Only Low-Dose CT detected sagittal clefts (represented by '+'). Referral US, US at Institution, Fetal MRI, and Combined (US + MRI) did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Flat Acetabula: Fetal MRI and Combined (US + MRI) detected flat acetabula (represented by '+'). Referral US and US at Institution did not detect it. The Venn diagram indicates overlap with Low-Dose CT. Enlarged Trochanters: All imaging modalities, including Low-Dose CT, detected enlarged trochanters. The Venn diagram indicates overlap among different modalities for this anomaly. In summary, the Venn diagram provides a visual representation of the distribution of detected anomalies among different imaging modalities, highlighting areas of overlap and exclusivity in anomaly detection.

4. Discussion

The present study aimed to comprehensively investigate antenatal musculoskeletal anomalies in pregnant females aged above 45 years with a history of previous deliveries involving babies with such anomalies. The cohort, consisting of 930 participants, exhibited a positive family history of congenital anomalies or genetic disorders, along with additional maternal risk factors such as diabetes, obesity, epilepsy, acquired Rubella, non-compliance with antenatal folic acid, and smoking during pregnancy. A recent study was conducted by Divya et al, they found that out of total 7268 babies delivered, 116 babies were found to have anomalies. Thirty-two of these had musculoskeletal defects. They concluded that better maternal care and improved standards of living have very little effect on the overall frequency of congenital malformations.[15] Another study by Prajkta et al was conducted on 1822 births, the total prevalence of major congenital anomalies was 230.51 (170.99–310.11) per 10 000 births. At the end of the study they identified the need for a well-defined national program with components of prevention, care and surveillance to prevent such anomalies.[16] It is important to establish a neonatal screening and identification of musculoskeletal malformations. This is helpful as timely detection and early intervention for many of these conditions can avoid permanent functional impairment in these children, as documented by Zhu et al.[17]

The sensitivity analysis revealed varying degrees of accuracy among different imaging modalities in detecting musculoskeletal anomalies. Referral Ultrasound (US) demonstrated a sensitivity of 61.3%, while US conducted at the institution exhibited a higher sensitivity at 79.1%. Fetal Magnetic Resonance Imaging (MRI) showed a sensitivity of 76.6%, and the combined use of US and MRI enhanced sensitivity to 82.6%. These findings suggest that combining imaging modalities, particularly US and MRI, may offer improved accuracy in identifying antenatal musculoskeletal anomalies. A study conducted by Roy et al, stated that For MSK abnormalities, fetal MRI and US exhibit similar sensitivity. Low-dose CT may offer more information in certain situations. Compared to US, fetal MRI found more non-MSK abnormalities in other organ systems. When multimodality imaging was used to combine all the data from MRI, US, and CT, if needed, the sensitivity for diagnosing musculoskeletal anomalies was eventually 89.2% (95% CI: 83.4% to 95.0%) and for additional anomalies in other organs and systems, it was 81.4%.[18] another study by Xianyun et al reported that 127 pregnant women who had fetuses suspected of having vertebral abnormalities on US examination participated in a single-center, retrospective study; the women also had fetal MRI screening. When identifying prenatal vertebral abnormalities, comparisons were made between MRI and US in terms of diagnostic accuracy and confidence. The diagnosis of prenatal vertebral abnormalities is more confident and accurate when done with fetal vertebral MRI. This

result suggests that fetal MRI adds to the data from US and that, in certain cases, MRI can be a useful adjunct when US is either unable to reach a definitive diagnosis or its accuracy is in question. Therefore, prenatal counseling and management decisions may benefit from the use of MRI.[19]

The specificity analysis emphasized the ability of each imaging modality to correctly identify cases without musculoskeletal anomalies. Referral US displayed a specificity of 94.6%, US at Institution exhibited a higher specificity at 98.0%, and Fetal MRI showcased an impressive specificity of 98.6%. The combined use of US and MRI also yielded a specificity of 98.6%, underscoring the reliability and specificity of each imaging technique. a prospective, blinded case-control research that included women who had an uneventful pregnancy and those who had a singleton pregnancy with fetal congenital anomalies found on clinical ultrasonography. showed that in 22.2% of fetuses with CNS abnormalities, MRI was more sensitive than ultrasonography and offered extra information that affected the prognosis, counseling, or care. When modest CNS abnormalities were seen, MRI yielded more false-positive diagnoses than ultrasonography.[20]

The investigation into combined sensitivity highlighted the enhanced diagnostic performance achieved by integrating findings from US and MRI. Referral US, Fetal MRI, and the combined use of US and MRI demonstrated sensitivities of 61.3%, 76.6%, and 82.6%, respectively. This collaborative approach leveraging both US and MRI holds promise for improving the overall sensitivity in detecting antenatal musculoskeletal anomalies. a historical cohort study involving all expectant mothers who were recommended for fetal magnetic resonance imaging (MRI) according to prenatal US screening results indicating craniofacial abnormalities. We evaluated the consistency and inconsistencies between prenatal diagnostic US, MRI, and postnatal diagnosis. found that MRI is helpful for evaluating fetal craniofacial abnormalities in the antenatal stage and could be a helpful supplement to US in the prenatal work-up for these conditions.[21]

The Receiver Operating Characteristic (ROC) curve analysis provided a nuanced understanding of the trade-offs between sensitivity and specificity across different diagnostic thresholds. The iterative exploration of thresholds beyond 0.3 up to 0.9 offered insights into how these imaging modalities perform across a spectrum of diagnostic criteria, facilitating a more informed and tailored approach to antenatal musculoskeletal anomaly detection. A recent meta-analysis was conducted by Mascio et al revealed that the rate of a CNS abnormalities identified only on MRI in fetuses receiving specialized neurosonography is lower than previously reported. Although the results of this review indicate that MRI performed in the third trimester may be associated with a better detection rate for some types of anomaly, such as cortical, white matter, and intracranial hemorrhagic anomalies, early MRI has an excellent diagnostic performance in identifying additional CNS anomalies.

The presence or absence of specific skeletal anomalies across various imaging modalities. This detailed breakdown underscored the strengths and unique contributions of each imaging modality in detecting specific skeletal anomalies, providing valuable insights for clinical decision-making. The log-fold change values further elucidated the magnitude of change in detection compared to the reference, emphasizing the performance differences among imaging modalities. The Chord diagram visually represented the overlap and exclusivity of detected anomalies among different imaging modalities. The diagram showcased relationships, correlations, and shared findings, contributing to a comprehensive understanding of the diagnostic landscape. A recent study demonstrated how MRI can be used in addition to prenatal ultrasound. When it comes to foetal spinal imaging, magnetic resonance imaging (MRI) can be useful in

distinguishing between isolated and complex abnormalities. This distinction can be important for prenatal and postnatal care, as complex abnormalities may be associated with unfavorable outcomes. Based on preliminary findings, MRI may provide a more accurate diagnosis in some cases than ultrasound in certain situations. To better visualize the foetal skeleton and understand the advantages of MRI over conventional ultrasound, more work must be put into improving MRI techniques.[22]

The study evaluates the clinical performance of different imaging modalities (MRI, CT, and US) in diagnosing antenatal musculoskeletal anomalies. By conducting a prospective cohort study and comparing the sensitivity and specificity of these modalities, the study assesses their diagnostic accuracy and effectiveness in identifying fetal defects. Clinical performance evaluation involves analyzing the ability of each imaging modality to accurately detect musculoskeletal anomalies, which is crucial for providing expectant mothers with reliable diagnostic information and guiding clinical management decisions. Effective prenatal screening and diagnosis of musculoskeletal anomalies are essential for malpractice prevention. By assessing the diagnostic performance of MRI, CT, and US, the study aims to identify the most reliable imaging modality for detecting fetal defects. Ensuring accurate and timely diagnosis of musculoskeletal anomalies can help healthcare providers mitigate the risk of malpractice claims by providing expectant mothers with appropriate medical care and management options based on reliable diagnostic information. The study examines the clinical impact and outcome of using different imaging modalities in diagnosing antenatal musculoskeletal anomalies. By comparing the sensitivity and specificity of MRI, CT, and US, the study provides insights into the diagnostic accuracy and effectiveness of each modality. Understanding the clinical impact and outcome of different imaging approaches is crucial for optimizing prenatal care practices and ensuring the best possible outcomes for both mothers and babies.

Strengths of the Study:

The use of a prospective cohort design enhances the reliability of the study by following participants over time, allowing for the collection of detailed information and minimizing recall bias. The inclusion of 930 pregnant females provides a substantial sample size, contributing to the statistical power of the study and allowing for more robust conclusions. Clear and well-defined inclusion and exclusion criteria contribute to the study's internal validity, ensuring that participants meet specific criteria relevant to the research question. The inclusion of three different imaging modalities (MRI, CT, and US) allows for a comprehensive assessment of musculoskeletal anomalies, providing a more thorough understanding of diagnostic capabilities. Adherence to ethical guidelines, obtaining informed consent, and obtaining Institutional Review Board (IRB) approval demonstrate a commitment to ethical conduct, ensuring the protection of participants' rights and privacy. The study collected detailed information on maternal risk factors, allowing for a comprehensive analysis of potential associations between these factors and musculoskeletal anomalies. The use of advanced imaging systems, such as the 3 Tesla Philips Ingenia MRI and 256-slice Brilliance iCT scanner, ensures high-quality imaging and enhances the accuracy of musculoskeletal anomaly detection. The use of a detailed and standardized data collection form contributes to data consistency and minimizes variability in recording information. The study employs both descriptive statistics for a comprehensive overview and analytical approaches, including univariate and multivariate analyses, to explore associations and identify independent contributors to musculoskeletal anomalies.

Limitations:

The exclusion of certain groups (e.g., individuals with contraindications for diagnostic modalities or those unwilling to provide informed consent) may introduce selection bias, limiting the generalizability of findings. The study's setting in a tertiary hospital in Riyadh, KSA, may limit the generalizability of results to other populations or healthcare settings. The exclusion of neonates lost to follow-up and participants not willing or able to comply with study requirements may introduce bias and affect the completeness of data. Exclusion of participants with incomplete data for investigation modalities may limit the completeness of the dataset and potentially introduce bias. The study conducted between May 2022 and October 2023 may have a relatively short time frame, and longer follow-up periods could provide additional insights into musculoskeletal anomalies. The reliance on self-reporting for maternal risk factors may introduce information bias, and the accuracy of reported risk factors may vary. While efforts to minimize radiation exposure were mentioned, the potential risks associated with CT scans, especially in pregnant individuals, should be acknowledged. The reliance on advanced imaging technologies may limit the study's generalizability to settings with different imaging capabilities. The interpretation of imaging findings is subject to the expertise of the radiologists and may vary, impacting the consistency of results. The study did not provide information on the cost-effectiveness of the different imaging modalities, which could be a relevant consideration for healthcare decision-makers. The study excluded pregnancies complicated by intrauterine fetal demise without postmortem X-rays or autopsy, which may limit the exploration of anomalies associated with such cases. The study focused primarily on diagnostic performance and did not extensively explore clinical outcomes related to detected anomalies. The study did not provide detailed information on the specific low-dose CT protocol, and variations in protocols could impact radiation exposure and image quality. Given the focus on pregnant females aged above 45 years, the generalizability of findings to younger populations may be limited. Exclusion of cases where genetic evaluation was performed without musculoskeletal anomalies may overlook potential genetic contributors to anomalies. Any logistical challenges encountered during the research, such as scheduling difficulties or equipment malfunctions, were not explicitly discussed. The study did not address the long-term follow-up of participants and the potential development of musculoskeletal anomalies in offspring beyond the immediate postnatal period.

5. Conclusion

In conclusion, the results of this study offer valuable insights into the diagnostic performance of various imaging modalities for antenatal musculoskeletal anomalies. The findings suggest that a combined approach, integrating the strengths of US and MRI, may enhance diagnostic accuracy and completeness. The detailed analysis of sensitivity, specificity, and the visual representation of the diagnostic landscape provide a foundation for further discussions on the optimal strategy for antenatal musculoskeletal anomaly detection. In summary, the study contributes to clinical performance evaluation and malpractice prevention by assessing the diagnostic accuracy and effectiveness of MRI, CT, and US in diagnosing antenatal musculoskeletal anomalies. By providing insights into the clinical impact and outcome of using different imaging modalities, the study helps healthcare providers make informed decisions about prenatal screening and diagnostic strategies, ultimately improving patient care and reducing the risk of malpractice related to diagnostic errors or suboptimal imaging techniques.

References

1 Fiat F, Merghes PE, Scurtu AD, Almajan Guta B, Dehelean CA, Varan N, Bernad E. The Main Changes in Pregnancy-Therapeutic Approach to Musculoskeletal Pain. Medicina (Kaunas). 2022 Aug 17;58(8):1115. doi: 10.3390/medicina58081115. PMID: 36013582; PMCID: PMC9414568.

2 Aksoy S. Antenatal screening and its possible meaning from unborn baby's perspective. BMC Med Ethics. 2001;2:E3. doi: 10.1186/1472-6939-2-3. Epub 2001 May 22. PMID: 11389776; PMCID: PMC32195.

3 Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. Cochrane Database Syst Rev. 2015 Jul 14;2015(7):CD007058. doi: 10.1002/14651858.CD007058.pub3. PMID: 26171896; PMCID: PMC6464767.

4 Nawapun K, Phithakwatchara N, Jaingam S, Viboonchart S, Mongkolchat N, Wataganara T. Advanced ultrasound for prenatal interventions. Ultrasonography. 2018 Jul;37(3):200-210. doi: 10.14366/usg.18011. Epub 2018 May 2. PMID: 29852543; PMCID: PMC6044223.

5 Norouzi S, Tavafian SS, Cousins R, Mokarami H. Understanding risk factors for musculoskeletal disorders in Iranian housewives: Development of a comprehensive health promotion behavior model. BMC Public Health. 2023 Mar 31;23(1):617. doi: 10.1186/s12889-023-15518-w. PMID: 37004008; PMCID: PMC10064530.

6 Ježová M, Pavlovská D, Grochová I, Michenková A, Vlašín P. Skeletal dysplasias of the fetus and infant: comprehensive review and our experience over a 10-year period. Cesk Patol. 2023 Summer;59(2):68-79. English. PMID: 37468326.

7 Krakow D. Skeletal dysplasias. Clin Perinatol. 2015 Jun;42(2):301-19, viii. doi: 10.1016/j.clp.2015.03.003. Epub 2015 Apr 8. PMID: 26042906; PMCID: PMC4456691.

8 Krakow D, Lachman RS, Rimoin DL. Guidelines for the prenatal diagnosis of fetal skeletal dysplasias. Genet Med. 2009 Feb;11(2):127-33. doi: 10.1097/GIM.0b013e3181971ccb. PMID: 19265753; PMCID: PMC2832320.

9 Victoria T, Epelman M, Coleman BG, Horii S, Oliver ER, Mahboubi S, Khalek N, Kasperski S, Edgar JC, Jaramillo D. Low-dose fetal CT in the prenatal evaluation of skeletal dysplasias and other severe skeletal abnormalities. AJR Am J Roentgenol. 2013 May;200(5):989-1000. doi: 10.2214/AJR.12.9722. PMID: 23617480.

10 Krakow D, Alanay Y, Rimoin LP, Lin V, Wilcox WR, Lachman RS, Rimoin DL. Evaluation of prenatal-onset osteochondrodysplasias by ultrasonography: a retrospective and prospective analysis. Am J Med Genet A. 2008 Aug 1;146A(15):1917-24. doi: 10.1002/ajmg.a.32269. PMID: 18627037; PMCID: PMC2713784.

11 Cai X, Chen X, Wei X, Liu W, Hou X, Gong T, Zhu J, Haacke EM, Wang G. Use of magnetic resonance imaging in the diagnosis of fetal vertebral abnormalities in utero: a single-center retrospective cohort study. Quant Imaging Med Surg. 2022 Jun;12(6):3391-3405. doi: 10.21037/qims-21-1070. PMID: 35655821; PMCID: PMC9131323.

12 Adler-Levy Y, Yagel S, Nadjari M, Bar-ziv Y, Simanovsky N, Hiller N. Use of low dose computed tomography with 3D reconstructions for the prenatal evaluation of suspected skeletal dysplasia. Isr Med Assoc J. 2015 Jan;17(1):42-6. PMID: 25739176.

13 Chandarana H, Wang H, Tijssen RHN, Das IJ. Emerging role of MRI in radiation therapy. J Magn Reson Imaging. 2018 Dec;48(6):1468-1478. doi: 10.1002/jmri.26271. Epub 2018 Sep 8. PMID: 30194794; PMCID: PMC6986460.

14 Sohn YS, Kim MJ, Kwon JY, Kim YH, Park YW. The usefulness of fetal MRI for prenatal diagnosis. Yonsei Med J. 2007 Aug 31;48(4):671-7. doi: 10.3349/ymj.2007.48.4.671. PMID: 17722241; PMCID: PMC2628062.

15 Agrawal D, Mohanty BB, Sarangi R, Kumar S, Mahapatra SK, Chinara PK. Study of incidence and prevalence of musculoskeletal anomalies in a tertiary care hospital of eastern India. J Clin Diagn Res. 2014 May;8(5):AC04-6. doi: 10.7860/JCDR/2014/7882.4380. Epub 2014 May 15. PMID: 24995167; PMCID: PMC4079988.

16 Bhide P, Gund P, Kar A. Prevalence of Congenital Anomalies in an Indian Maternal Cohort: Healthcare, Prevention, and Surveillance Implications. PLoS One. 2016 Nov 10;11(11):e0166408. doi: 10.1371/journal.pone.0166408. PMID: 27832123; PMCID: PMC5104451.

17 Xiong Z, Zhao Z, Deng H, Qiu X, Li W, Chen X, Tang Y, Han S, Zhao J, Cai T, Liu X, Zeng S, Tang S. Screening for musculoskeletal system malformations and birth injuries in newborns: Results of a screening program in two hospitals in Shenzen, China. Pediatr Investig. 2022 Jun 20;6(3):156-162. doi: 10.1002/ped4.12334. PMID: 36203522; PMCID: PMC9523807.

18 Bisht RU, Belthur MV, Singleton IM, Goncalves LF. Accuracy of Multimodality Fetal Imaging (US, MRI, and CT) for Congenital Musculoskeletal Anomalies. Children (Basel). 2023 Jun 5;10(6):1015. doi: 10.3390/children10061015. PMID: 37371247; PMCID: PMC10297094.

19 Cai X, Chen X, Wei X, Liu W, Hou X, Gong T, Zhu J, Haacke EM, Wang G. Use of magnetic resonance imaging in the diagnosis of fetal vertebral abnormalities in utero: a single-center retrospective cohort study. Quant Imaging Med Surg. 2022 Jun;12(6):3391-3405. doi: 10.21037/qims-21-1070. PMID: 35655821; PMCID: PMC9131323.

20 Gonçalves LF, Lee W, Mody S, Shetty A, Sangi-Haghpeykar H, Romero R. Diagnostic accuracy of ultrasonography and magnetic resonance imaging for the detection of fetal anomalies: a blinded case-control study. Ultrasound Obstet Gynecol. 2016 Aug;48(2):185-92. doi: 10.1002/uog.15774. Epub 2016 Jul 10. PMID: 26444861; PMCID: PMC5987216.

21 Zemet R, Amdur-Zilberfarb I, Shapira M, Ziv-Baran T, Hoffmann C, Kassif E, Katorza E. Prenatal diagnosis of congenital head, face, and neck malformations-Is complementary fetal MRI of value? Prenat Diagn. 2020 Jan;40(1):142-150. doi: 10.1002/pd.5593. Epub 2019 Nov 11. PMID: 31664716.

22 Nemec U, Nemec SF, Krakow D, Brugger PC, Malinger G, Graham JM Jr, Rimoin DL, Prayer D. The skeleton and musculature on foetal MRI. Insights Imaging. 2011 Jun;2(3):309-318. doi: 10.1007/s13244-011-0075-6. Epub 2011 Feb 19. PMID: 22347955; PMCID: PMC3259321.