Universidade de Lisboa

Faculdade de Medicina

Avaliação ecográfica do crescimento fetal no final do 3º trimestre da gravidez de baixo risco

Ana Catarina Ferreira Policiano

Orientador: Professor Doutor Luís Fernando Pacheco Mendes da Graça

Tese especialmente elaborada para obtenção do grau de Doutor em Medicina, Ginecologia e Obstetrícia

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Fundação para a Ciência e a Tecnologia: SFRH/SINTD/92997/2013

2020

A impressão desta tese foi aprovada pelo Conselho Científico da Faculdade de Medicina de Lisboa em reunião de 21 de julho de 2020.

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O trabalho aqui apresentado foi realizado no Departamento de Obstetrícia, Ginecologia e Medicina da Reprodução do Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte e no *Hospital Clínic e Hospital Sant Joan de Déu, Universitat de Barcelona; BCNatal, Barcelona Center for Maternal Fetal and Neonatal Medicine*.

Para o Manuel e o Afonso,
a minha inspiração máxima e força inesgotável. Para que nunca deixem de lutar pelos seus sonhos.
Para o Lino,
pelo apoio e compreensão incondicionais. Pela sorte de um amor assim.
Para os meus pais,
pelo exemplo e por todas as oportunidades que me proporcionaram, porque lhes devo tudo o que sou.
Para todos os amigos e colegas,
que acreditaram em mim e tornaram este projeto possível.

One, remember to look up at the stars and not down at your feet.
Two, never give up work. Work gives you meaning and purpose, and life is empty without it.
Three, if you are lucky enough to find love, remember it is there and don´t throw it away.

Stephen Hawking

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ACKNOWLEDGEMENTS

Decidi realizar os agradecimentos na minha língua materna para não correr o risco de perder a dimensão emocional e o sentimento com a tradução.

Ao Professor Doutor Luís Graça, por ter acreditado em mim, pelo seu incentivo e motivação constantes para que todos os projetos fossem concluídos. O meu agradecimento por ter sido um mestre, na clínica e na ciência; pelo seu rigor científico e exigência, que me tornaram mais assertiva e persistente. Sempre que precisei de ponderar que caminho seguir, esteve lá com a sua experiência para me aconselhar, para não me deixar desistir, mesmo quando os objetivos pareciam tão longínquos e difíceis de atingir.

Ao Dr. Nuno Clode, que sem o ser na teoria, foi um verdadeiro co-orientador desta tese. Foi ele que fez despertar em mim o gosto pela Obstetrícia e pela investigação clínica; que me desafiou a embarcar neste projeto. Ao Dr. Nuno devo tantas ideias; a motivação para não me deixar ficar pelo simples e lutar para ir mais além, para tentar ser diferente e inovar. Além do seu espírito e inquietude contagiante que me motivaram ao longo dos anos e que foram cruciais para conseguir terminar o projeto, devo-lhe centenas de grávidas recrutadas para os estudos. Ele próprio recrutava nos seus períodos de consulta e motivava os colegas internos que com ele aprendiam a ser Obstetras. O meu agradecimento por todos os meses me perguntar "quantas grávidas já tínhamos?". A sua persistência, trabalho e dedicação foram um exemplo. Foi um privilégio fazer esta tese com a sua orientação.

Ao Lino, meu marido, por me ter dado o equilíbrio emocional, a tranquilidade e calma, que foram, inquestionavelmente, essenciais para tornar este projeto possível. Por ter sempre acreditado em mim, por ter sido compreensivo quando nem sempre estive tão disponível e presente. Por ter sido um verdadeiro companheiro de todos os dias; por vibrar com os meus sucessos e por me fazer vencer as dificuldades. Por perceber a minha paixão pela investigação, a minha necessidade de aprender mais e mais, de abraçar novos projetos e desafios, mas por fazer questão de todos os dias me mostrar o que é verdadeiramente importante. Ao Manuel e ao Afonso, os meus filhos, que tornaram este caminho ainda mais desafiante, por me fazerem olhar para o futuro com ainda mais vontade de aprender e tornar o mundo melhor.

Aos meus pais e irmão, por todas as oportunidades que me proporcionaram ao longo da vida e pelo seu exemplo de pessoas extraordinárias, que determinaram tudo o que sou hoje. Nada do que eu possa escrever consegue demonstrar o meu sentimento de gratidão para com eles. São um pilar fundamental na minha vida, sempre disponíveis para este projeto e tantos outros.

Ao Dr. Alexandre Valentim Lourenço, o meu orientador da Formação Específica, por ter acreditado em mim, quando eu própria ainda não sabia que queria ser ginecologista e obstetra e que queria concretizar este projeto. Pelo seu otimismo e disponibilidade, que me fizeram acreditar que a atividade de doutoranda e de interna são compatíveis e possíveis de realizar em paralelo.

Ao Professor Doutor Carlos Calhaz-Jorge, pela sua compreensão e apoio, enquanto Diretor de Departamento, na organização dos tempos dedicados à atividade doutoral e da formação específica.

À Dra. Luísa Pinto, por ser um modelo de profissional e de ser humano; pela sua generosidade e disponibilidade em contribuir para este projeto com a sua experiência, rigor e espírito crítico.

À Dra. Andreia Fonseca, Dra. Joana Barros, Dra. Diana Martins, Dra. Sara Vargas, Dra. Margarida Cal, Dra. Inês Reis, Dra. Catarina Reis de Carvalho e Dra. Inês Martins, "companheiras de maratonas de ecografias", pela sua disponibilidade e companheirismo na realização das centenas de exames ecográficos, sem os quais esta tese não seria possível. Quando se tem a oportunidade de partilhar trabalho com colegas-amigas tudo se torna mais fácil.

À Dra. Rita Rosado, Dra. Sara Pereira, Dra. Sofia Mendes, Dra. Rita Silva, Dra. Alexandra Meira, Dra. Susana Rego, Dra. Laura Cruz e Dra. Ana Dagge por terem colaborado no recrutamento de grávidas para o estudo aleatorizado.

Ao Professor Doutor Francesc Figueras, Professora Doutora Fatima Crispi, Professora Doutora Elisenda Eixarch, Dr. Jezid Miranda e Dra. Cristina Paules, com quem tanto aprendi durante o período de estágio no Hospital Clínic, em Barcelona. Foi uma oportunidade de excelência para melhorar as minhas capacidades na investigação clínica.

Ao Professor Doutor Jorge Mendes por ter sido incansável no seu contributo para a análise estatística dos dados dos diversos estudos, sem o qual este projeto não teria sido possível.

À Dra. Ana Aguiar, Dra. Cláudia Araújo e Dra. Catarina Castro, três amigas e médicas extraordinárias, que sempre acreditaram em mim e com as quais sempre pude contar. O seu otimismo e a sua energia contagiante foram inspiradores.

A todos os elementos do Departamento de Obstetrícia, Ginecologia e Medicina da Reprodução do Hospital de Santa Maria, pelo seu apoio e solidariedade fundamentais para este projeto. Este agradecimento é dirigido não só aos colegas médicos, mas também aos enfermeiros, assistentes operacionais e administrativos, pela sua disponibilidade e apoio constantes, sem os quais não seria possível a conclusão de todos os estudos incluídos neste projeto.

Um agradecimento muito particular a todas as grávidas pela sua boa vontade em deslocar-se de forma não remunerada ao hospital para a realização de ecografias adicionais à vigilância preconizada para a gravidez de baixo risco. Sem a sua compreensão e disponibilidade em consentir participar nos estudos desta tese, nada teria sido possível.

ABBREVIATIONS

AC	Abdominal circumference
ACOG	American College of Obstetricians and Gynecologists
AFI	Amniotic fluid index
AGA	Appropriate for gestational age
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
BPD	Biparietal diameter
CC	Corpus callosum
CI	Confidence interval
CIX	Cephalic index
CPR	Cerebroplacental ratio
CRL	Crown rump length
CTG	Cardiotocography
DGS	Direção-Geral da Saúde
EFW	Estimated fetal weight
EPF	Estimativa de peso fetal
FGR	Fetal growth restriction
FL	Femur length
GM	Grey matter
GOs	Gynecologists/Obstetricians
GPs	General practitioners
GROW	Gestation-Related Optimal Weight

HC	Head circumference
HSM-CHULN	Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte
Inter-CC	Inter-observer Pearson´s correlation coefficient
Intra-CC	Intra-observer Pearson´s correlation coefficient
IQR	Interquartile range
ISUOG	The International Society of Ultrasound in Obstetrics and Gynecology
IVF	In vitro fertilization
LIG	Leve para a idade gestacional
LGA	Large for gestational age
MCA	Middle cerebral artery
MGF	Medicina Geral e Familiar
MR	Magnetic resonance
MWC	Maternal waist circumference
NICU	Neonatal intensive care unit
NSG	Neurosonography
OFD	Occipitofrontal diameter
PE	Preeclampsia
PI	Pulsatility index
RCF	Restrição do crescimento fetal
ROC	Receiver-operating characteristics
RR	Risk ratio
SD	Standard deviation
SDP	Single deepest vertical pocket
SFD	Symphysis-uterine fundus distance
SGA	Small for gestational age

STATA	Statacorp, College Station, Texas, US
UA	Umbilical artery
UtA	Uterine artery
WHO	World Health Organization
WM	White matter
α-RC	Crohnbach´s α reliability coefficient

RESUMO

A avaliação da estimativa do peso fetal (EPF) durante o exame ecográfico do terceiro trimestre na gravidez de baixo risco, é considerada o método mais eficaz de diagnóstico de restrição do crescimento fetal (RCF), permitindo uma adequada vigilância e programação do parto. Contudo, não existe consenso relativamente à necessidade de um exame ecográfico de rotina, durante o terceiro trimestre da gravidez de baixo risco, com o objetivo de rastreio de RCF, nem de qual será a melhor idade gestacional para a sua realização. Até à data, a realização deste exame não demonstrou vantagens em termos de desfechos perinatais. Não obstante, os casos de RCF tardias não diagnosticados anteparto representam uma proporção significativa de mortes fetais no termo e estão associados a um maior risco de desfechos neonatais adversos, comparativamente aos casos de RCF diagnosticados durante a gravidez.

O objetivo global desta tese foi a investigação quanto ao melhor método de rastreio de RCF tardia, em grávidas de baixo risco, incluindo-se para tal cinco projetos.

O **projeto I** consistiu num estudo retrospetivo em que foi comparada a via de parto e a taxa de admissão de recém-nascidos nas unidades de cuidados intensivos neonatais, entre aqueles com peso adequado para a idade gestacional e os leves para a idade gestacional, de gestações de termo e de baixo risco. Um total de 1429 grávidas foi incluído, com uma taxa de 11% de leves para a idade gestacional (LIG), definidos como recém-nascidos ≥ 37 semanas com peso ao nascimento < percentil 10. Os LIG associaram-se a maior taxa de cesariana por suspeita de hipóxia fetal intraparto (18/151 *vs* 8/1202, $p < 0{,}001$) e maior taxa de admissão nas unidades de cuidados intensivos neonatais (16/151 *vs* 18/1202, $p < 0{,}001$). Entre os LIG, verificámos que os que foram diagnosticados por ecografia anteparto apresentaram menor taxa de parto instrumental/cesariana por suspeita de hipóxia fetal intraparto comparativamente com o grupo de LIG que não foram diagnosticados anteparto (3/31 *vs* 39/120, $p = 0{,}01$).

O **projeto II** correspondeu a um estudo prospetivo que avaliou a reprodutibilidade das biometrias fetais ecográficas (diâmetro biparietal, perímetro cefálico, perímetro abdominal e comprimento do fémur) realizadas às 35-37 semanas de gestação. Um total de 197 grávidas foi incluído e cada uma foi submetida a três avaliações ecográficas sucessivas, uma por um ecografista e duas por um outro ecografista, correspondendo a um total de 591 avaliações ecográficas. Registaram-se coeficientes de correlação intra e inter-observador muito elevados para todas as medidas avaliadas (todos com valores superiores a 0,85), demonstrando-se elevada reprodutibilidade intra e inter-observador da ecografia do terceiro trimestre realizada às 35-37 semanas de gestação.

O **projeto III** foi um estudo prospetivo observacional que teve como objetivo comparar o conhecimento e prática clínica entre os Ginecologistas-Obstetras (GOs) e os médicos de Medicina Geral e Familiar (MGF) portugueses relativamente ao rastreio de RCF em grávidas de baixo risco, através da aplicação de questionários, tendo-se conseguido um total de 573 respostas. Verificámos que uma maior proporção de GOs (38%) selecionaram a ecografia às 35-37 semanas como o melhor momento no terceiro trimestre para rastreio de RCF, comparativamente com a proporção de médicos de MFG (10%) ($p < 0,001$).

O **projeto IV** consistiu num estudo prospetivo aleatorizado que comparou a acuidade diagnóstica e os desfechos perinatais entre um grupo de controlo, que realizou apenas a ecografia de rotina no terceiro trimestre, às 30-33 semanas de gestação, e um grupo de estudo que realizou uma ecografia adicional às 35-37 semanas, incluindo-se um total de 1093 grávidas de baixo risco. A ecografia realizada às 35-37 semanas registou uma acuidade diagnóstica global para rastreio de RCF de 94%. O coeficiente de correlação de Spearman foi superior entre o percentil da EPF às 35-37 semanas e o percentil do peso ao nascimento ($\rho = 0,75$), comparativamente com o coeficiente de correlação entre o percentil da EPF às 30-33 semanas e o percentil do peso ao nascimento ($\rho = 0,44$). O grupo de estudo registou também melhores desfechos perinatais, nomeadamente uma menor taxa de partos vaginais instrumentados por suspeita de hipóxia fetal intraparto (24,4% *vs* 39,3%, $p = 0,005$) e menor taxa de cesarianas por suspeita de hipóxia fetal intraparto (16,8% *vs* 38,8%, $p < 0,001$), comparativamente com o grupo de controlo.

O **projeto V** constou de um estudo prospetivo com o objetivo de investigar se a neurossonografia permite detetar alterações da substância branca e cinzenta na RCF. Com um total de 318 fetos submetidos ao estudo neurossonográfico, foi possível demonstrar que as RCF tardias apresentam diferenças em termos de desenvolvimento cortical e do corpo caloso, comparativamente com os casos de controlo, sugerindo que a neurossonografia permite demonstrar algumas diferenças de reorganização cerebral na RCF.

Em conclusão, um exame ecográfico mais tardio durante o terceiro trimestre (35-37 semanas de gestação) tem precisão e maior correlação com o percentil do peso ao nascimento do que um exame mais precoce no terceiro trimestre, podendo ainda contribuir para diminuir desfechos perinatais adversos. As diferenças nos padrões neurossonográficos entre fetos com crescimento adequado para a idade gestacional e com RCF reforçam o conceito de que uma abordagem combinada que inclua biometrias fetais, bem como outros marcadores clínicos, biológicos e/ou imagiológicos, pode contribuir para otimizar o rastreio de RCF e os desfechos perinatais.

Palavras-chave: Rastreio ecográfico no terceiro trimestre, gravidez de baixo risco, restrição de crescimento fetal, estimativa de peso fetal, desfechos perinatais adversos.

RESUMO EXTENSO

A restrição de crescimento fetal (RCF) não diagnosticada constitui um dos achados mais frequentemente encontrados em mortes fetais de termo inexplicadas e está associada a um maior risco de desfechos perinatais adversos. A avaliação da estimativa de peso fetal durante o exame ecográfico no terceiro trimestre é considerada o método mais eficaz para o seu diagnóstico. No entanto, na gravidez de baixo risco, a medição da altura uterina é o método mais utilizado, sendo um método de sensibilidade variável. Não existe consenso relativamente à necessidade de um exame ecográfico de rotina, durante o terceiro trimestre, nem de qual será a melhor idade gestacional para a sua realização. Em Portugal, de acordo com o Programa Nacional Para a Vigilância da Gravidez de Baixo Risco da Direção Geral da Saúde (DGS), está recomendada a realização de uma ecografia de rotina às 30-33 semanas.

O objetivo global desta tese foi a investigação quanto ao melhor método de rastreio de restrição de crescimento fetal tardia, em grávidas de baixo risco.

Foi realizado um estudo retrospetivo em que foi comparada a via de parto e a taxa de admissão de recém-nascidos nas unidades de cuidados intensivos neonatais, entre aqueles com peso adequado para a idade gestacional e os leves para a idade gestacional, de gestações de termo e de baixo risco. Um total de 1429 grávidas foi incluído, com uma taxa de 11% de leves para a idade gestacional (LIG), definidos como recém-nascidos ≥ 37 semanas com peso ao nascimento < percentil 10. A taxa de deteção de LIG pela ecografia de rotina realizada às 30-33 semanas foi de 21%. Os LIG associaram-se a maior taxa de cesariana por suspeita de hipóxia fetal intraparto (18/151 *vs* 8/1202, $p < 0{,}001$) e maior taxa de admissão nas unidades de cuidados intensivos neonatais (16/151 *vs* 18/1202, $p < 0{,}001$). Entre os LIG, verificámos que os que foram diagnosticados por ecografia anteparto apresentaram menor taxa de parto instrumental/cesariana por suspeita de hipóxia fetal intraparto comparativamente com o grupo de LIG que não foram diagnosticados anteparto (3/31 *vs* 39/120, $p = 0{,}01$).

Com o objetivo de otimizar o rastreio de RCF, testámos a hipótese de uma melhor acuidade diagnóstica de uma ecografia realizada numa fase mais tardia do terceiro trimestre (35-37 semanas). De forma prospetiva, foi avaliada a reprodutibilidade das biometrias fetais ecográficas (diâmetro biparietal, perímetro cefálico, perímetro abdominal e comprimento do fémur) realizadas às 35-37 semanas de gestação. Um total de 197 grávidas foi incluído e cada uma foi submetida a três avaliações ecográficas sucessivas, uma por um ecografista e duas por um outro ecografista, correspondendo a um total de 591 avaliações ecográficas. Registaram-se coeficientes de correlação intra e inter-observador muito elevados para todas as medidas avaliadas (todos com valores superiores a 0,85), demonstrando-se elevada reprodutibilidade intra e inter-observador da ecografia do terceiro trimestre realizada às 35-37 semanas de gestação. Os resultados deste estudo foram importantes para validar a realização de ecografias do estudo aleatorizado por diferentes ecografistas, sem prejuízo da sua precisão.

Realizámos um estudo prospetivo observacional com o objetivo de comparar o conhecimento e a prática clínica entre os Ginecologistas-Obstetras (GOs) e os médicos de Medicina Geral e Familiar (MGF) portugueses relativamente ao rastreio de RCF em grávidas de baixo risco, através da aplicação de questionários, tendo-se conseguido um total de 573 respostas. Verificámos que uma maior proporção de GOs (38%) selecionaram a ecografia às 35-37 semanas como o melhor momento no terceiro trimestre para rastreio de RCF, comparativamente com a proporção de médicos de MFG (10%) (p < 0,001). Embora não tenha sido perguntado aos médicos se tinham conhecimento da Norma da DGS, nem dos motivos das suas escolhas de resposta ao questionário, é evidente a variação existente nos seus conhecimentos e prática clínica. Esta variação reflete a controvérsia do tema e reforça a necessidade de mais estudos no sentido de otimizar o rastreio de RCF tardia, na gravidez de baixo risco.

A realização de um estudo prospetivo aleatorizado permitiu comparar a acuidade diagnóstica e os desfechos perinatais entre um grupo de controlo, que realizou apenas a ecografia de rotina no terceiro trimestre, às 30-33 semanas de gestação, e um grupo de estudo que realizou uma ecografia adicional às 35-37 semanas, incluindo-se um total de 1093 grávidas de baixo risco. A ecografia realizada às 35-37 semanas registou uma acuidade diagnóstica global para rastreio de RCF de 94% e uma área sob a curva de 90%. O coeficiente de correlação de Spearman foi superior entre o percentil da EPF às 35-37 semanas e o percentil do peso ao nascimento (ρ = 0,75), comparativamente com o coeficiente de correlação entre o percentil da EPF às 30-33 semanas e o percentil do peso ao nascimento (ρ = 0,44). Estes resultados estão de acordo com outros estudos que demonstraram melhor acuidade diagnóstica de RCF de uma ecografia realizada mais tarde no terceiro trimestre, em comparação com uma ecografia mais precoce. Por um lado, quanto mais próxima do parto for realizada a estimativa de peso fetal, maior a probabilidade de estar próxima do percentil de peso ao nascimento. Por outro lado, temos de considerar a possibilidade de alguns fetos desacelerarem o seu crescimento após as 30-33 semanas, motivo pelo qual só seriam diagnosticados pela ecografia mais tardia. O facto de ponderarmos adiar a ecografia de rotina do terceiro trimestre para as 35-37 semanas implica refletir na possibilidade de diagnosticarmos "demasiado tarde" casos de RCF e que tal implique acréscimo de mortalidade perinatal. Apesar das limitações em termos de poder estatístico da nossa amostra para avaliar este desfecho, outros autores já demonstraram que a mortalidade fetal aumenta sobretudo após as 37 semanas.

O grupo de estudo registou também melhores desfechos perinatais, nomeadamente uma menor taxa de partos vaginais instrumentados por suspeita de hipóxia fetal intraparto (24,4% *vs* 39,3%, p =

0,005) e menor taxa de cesarianas por suspeita de hipóxia fetal intraparto (16,8% *vs* 38,8%, $p < 0,001$), comparativamente com o grupo de controlo. As diferenças registadas nos desfechos perinatais reforçam os resultados do estudo retrospetivo em como a deteção anteparto de casos de RCF permite uma vigilância e orientação do parto mais adequada, o que poderá contribuir para evitar a necessidade de intervenção obstétrica urgente. Provavelmente, no grupo de estudo, a programação mais precoce do parto no grupo de grávidas em que se identificou a presença de RCF evitou que estes fetos fossem submetidos a um trabalho de parto apenas às 41 semanas, para o qual poderiam não ter reserva placentária suficiente. No grupo de estudo, a realização de uma ecografia adicional às 35-37 semanas retrata a utilidade de um conceito de avaliação de velocidade de crescimento fetal, por oposição ao conceito de avaliação do tamanho fetal. Apesar das limitações em termos de constrangimentos de recursos económicos e humanos na adoção deste conceito de velocidade de crescimento no rastreio de RCF, há que pesar os potenciais benefícios clínicos e de custos, em termos de diminuição de intervenção obstétrica urgente.

Foi realizado ainda um estudo prospetivo com o objetivo de investigar se a neurossonografia permite detetar alterações da substância branca e cinzenta na RCF. Com um total de 318 fetos submetidos ao estudo neurossonográfico, foi possível demonstrar que as RCF tardias apresentam diferenças em termos de desenvolvimento cortical e do corpo caloso, comparativamente com os casos de controlo, sugerindo que a neurossonografia permite demonstrar algumas diferenças de reorganização cerebral na RCF.

Em conclusão, num país que reconhece a importância da realização de rastreio ecográfico de RCF durante o terceiro trimestre da gravidez de baixo risco, os dados obtidos nesta tese reforçam as conclusões de estudos internacionais de que um exame ecográfico mais tardio durante o terceiro trimestre (35-37 semanas de gestação) tem precisão e maior correlação com o percentil do peso ao nascimento do que um exame mais precoce no terceiro trimestre, podendo ainda contribuir para diminuir desfechos perinatais adversos. As diferenças nos padrões neurossonográficos entre fetos com crescimento adequado para a idade gestacional e com RCF reforçam o conceito de que uma abordagem combinada que inclua biometrias fetais, bem como outros marcadores clínicos, biológicos e/ou imagiológicos, pode contribuir para otimizar o rastreio de RCF e os desfechos perinatais.

SUMMARY

Sonographic estimation of fetal weight (EFW) during the third trimester in low-risk pregnancies is considered the most effective method for the diagnosis of fetal growth restriction (FGR) permitting a close surveillance and timely delivery. However, there is no consensus on the need for a routine third trimester ultrasound nor on the best gestational age to perform it with the aim of screening for FGR in low risk pregnancies. So far, evidence has not provided data showing objective advantages on perinatal outcomes. Nonetheless, undiagnosed late FGR constitutes a significant proportion of term stillbirths and undiagnosed FGR is associated with a higher risk of adverse neonatal outcomes when compared to FGR diagnosed during pregnancy.

The overall aim of this thesis, which includes five studies, was to investigate the best screening method for late FGR in low risk pregnancies.

Study I was a retrospective study with the aim of comparing delivery route and admission rate to neonatal intensive care unit between small- and appropriate-for-gestational-age babies among term low risk pregnancies. A total of 1429 pregnancies was included and 11% had a small for gestational age baby (SGA), defined as babies delivered at ≥ 37 weeks with birthweight < 10^{th} centile. SGA were associated with a higher rate of cesarean sections for non-reassuring fetal status (18/151 *vs* 8/1202, $p < 0.001$) and a higher rate of admissions to neonatal intensive care unit (16/151 *vs* 18/1202, $p < 0.001$) compared to appropriate-for-gestational-age. Within the SGA group, antepartum detected fetuses were associated with lower rate of operative deliveries for non-reassuring fetal status when compared to the undetected group (3/31 *vs* 39/120, $p = 0.01$).

Study II was a prospective study that evaluated the reproducibility of fetal measurements (biparietal diameter, head circumference, abdominal circumference and femur length) at 35-37 weeks' ultrasound. A total of 197 women was included and each was submitted to three scans at the same appointment, one by one operator and two by a different operator, corresponding to a total of 591 ultrasound evaluations. We have registered very high intra- and inter-observer correlation coefficients for all four biometric parameters (all of them above 0.85), demonstrating high intra- and inter-observer reproducibility for the 35^{th}-37^{th} weeks' gestation third trimester ultrasound.

Study III was a prospective observational study with the aim of comparing knowledge and practices surrounding third trimester screening of FGR in low risk pregnancies among Portuguese Gynecologists/Obstetricians (GOs) and General Practitioners (GPs), based on the completion of a survey, with a total of 573 respondents. A higher proportion of GOs (38%) selected 35-37 weeks as the best time to perform the third trimester ultrasound screening of FGR when compared to GPs (10%) ($p < 0.001$).

Study IV was a prospective randomized trial that compared accuracy and perinatal outcomes between a control group with routine third trimester ultrasound at 30-33 weeks and another group with an additional ultrasound at 35-37 weeks' gestation, with a total of 1093 low risk pregnant women included. The ultrasound at 35-37 weeks' gestation had an overall accuracy of screening for FGR of 94%. Spearman´s correlation coefficient was higher between the EFW centile at 35-37 weeks' ultrasound and birthweight centile ($\rho = 0.75$) than the correlation coefficient between the EFW centile at 30-33 weeks' ultrasound and birthweight centile ($\rho = 0.44$). The study group had better perinatal outcomes, namely a lower rate of operative vaginal deliveries for non-reassuring fetal status (24.4% *vs* 39.3%, $p = 0.005$) and a lower rate of cesarean deliveries for non-reassuring fetal status (16.8% *vs* 38.8%, $p < 0.001$), compared to the control group.

Study V was a prospective study with the aim of exploring whether neurosonography can detect differences in grey and white matter in small fetuses. With a total of 318 fetuses submitted to neurosonography, we have provided evidence that late onset small fetuses presented differences in cortical and corpus callosum development compared to controls, suggesting certain degree of brain reorganization that could be demonstrated by ultrasound.

In conclusion, later ultrasound during the third trimester (35-37 weeks' gestation) is precise, has higher correlation with birthweight than an earlier ultrasound and may also contribute to a decrease in adverse perinatal outcomes. The differences in neurosonographic patterns between appropriate weight and FGR reinforce the concept that a combined approach that includes biometry as well as other clinical, biological and/or imaging markers may improve FGR screening and outcome.

Keywords: Third-trimester ultrasound screening, low risk pregnancy, fetal growth restriction, estimated fetal weight, adverse perinatal outcome.

CHAPTER 1

GENERAL INTRODUCTION

1. Third trimester screening of fetal growth

Fetal size and growth trajectories are important indicators of underlying fetal health. Growth anomalies have long been diagnosed after birth, by weighing the newborn, with the use of terminologies such as low birthweight, macrosomia, SGA and large for gestational age (LGA).[1] Both extremes of fetal growth are associated with adverse perinatal outcomes. FGR is the second most common finding associated with stillbirth,[2,3] and undiagnosed late FGR constitutes a significant proportion of term stillbirths.[4,5] Furthermore, undiagnosed FGR is associated with a higher risk of adverse neonatal outcomes (5-minute Apgar score < 4, neonatal seizures, acidosis and neonatal death), when compared to diagnosed FGR.[4,5]

For all these reasons, antenatal screening and diagnosis of fetal growth abnormalities are important components of modern-day obstetrics. The most commonly used screening tool in low risk populations is serial measurement of fundal height, the distance between the upper border of the pubic symphysis and the uterine fundus. This method has a low sensitivity for the diagnosis of FGR and macrosomia, but a high specificity for the latter, particularly when defined as birthweight above 4500g.[6-8] There is still much scientific uncertainty surrounding the benefit of third trimester sonographic screening of FGR in low-risk pregnancies, as well as on the ideal time to perform it.[9] It may be argued that the results of these studies have limited contemporary validity as they have used outdated surrogates of fetal growth or protocols in which FGR diagnosis elicited no change in management. The main argument against a routine third trimester ultrasound is the possibility that it could induce overdiagnosis of FGR, since a significant proportion of these fetuses are constitutively SGA. SGA are not pathological fetuses, but it is very difficult to distinguish them from FGR and they would be put at risk of unnecessary obstetric intervention, iatrogenic preterm deliveries, labor induction and eventually more cesarean deliveries. On the other hand, in the absence of a third trimester ultrasound, undetected FGR may not have enough placental respiratory reserve to withstand pregnancy up to 41 weeks and the demands of labor at that gestational age which would result in higher cesarean deliveries and potentially more admissions to neonatal intensive care unit (NICU). Despite this, it is routinely used in many countries during the early third trimester, a strategy that has recently been endorsed by the World Health Organization (WHO).[10]

2. Sonographic assessment of fetal size and growth

Whichever method is used for screening, fetal ultrasound has achieved a central role in modern-day diagnosis and management of fetal growth deviations. The most commonly used sonographic definition of SGA is an EFW below the 10^{th} percentile.[11] The rationale behind using 10^{th} percentile cut-off for weight-for-age distribution is similar to that of statistical inference using a *p*-value cut-off of 0.05 for rejecting the null hypothesis. It is also analogous to the concept of mean weight ± standard deviations as cut-offs for abnormal weight-for-age.[1,12] Although 10% of normal fetuses will fall below the 10th percentile (false positives), the probability that a fetus who is not achieving its growth potential (i.e. has growth restriction) is included in this category is much higher, and the magnitude of probability is related to the severity of the disease process.[1,13] An important feature underlying this concept is the establishment of growth charts using only ´normal` fetuses. Another important understanding is that accurate knowledge of gestational age is essential for fetal growth assessment. Dating pregnancies by early ultrasound examination at 8–14 weeks, based on measurement of the fetal crown rump length (CRL), appears to be the most reliable method to establish gestational age.[14-16] When the expected delivery date has been established by an accurate early scan, subsequent scans should not be used to recalculate the gestational age. Therefore, serial scans can be used to determine if interval growth has been normal.

3. Sonographic parameters

A variety of sonographic parameters may be used to diagnose fetal growth abnormalities. Abdominal circumference (AC) is considered to be the most sensitive isolated parameter in prediction of SGA,[17] especially in low risk pregnancies and term fetuses, and has a good correlation with FGR and with morbidity parameters, such as hypoxia and acidemia.[18,19] However, EFW using formulas that include head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) is considered the most accurate biometric parameter, notwithstanding a random error that can reach 15% (close to 400 g in an average term fetus). Errors appear to be higher for small and large fetuses.[20]
The majority of charts for sonographic EFW are designed to identify fetal growth abnormalities that occur during the third trimester.[21,22] Second trimester fetal growth is usually assessed by longitudinal evaluations of the biparietal diameter.[20]

4. Fetal growth curves

Accurate ultrasound and birthweight standards are essential for the detection of abnormal fetal growth, and the choice of the standard has the potential to affect the percentage of fetuses identified as SGA or LGA.

Birthweight standards before term are often not fully representative of normality, because a great proportion of preterm newborns are also growth restricted, but the prenatal diagnosis was missed. A major area of debate is whether a single universal growth reference chart should be used, or whether parental, ethnic and regional differences in fetal growth are best represented by customizing growth curves to individual characteristics.

'Intergrowth 21` is the name of a research project based at the University of Oxford, which produced a single and universally applicable growth standard, derived from a multi-ethnic population of eight countries.[21] The underlying concept is that potential growth is similar in human beings, and that differences observed across countries and populations are mainly explained by variations in nutritional and health status. The standards therefore represent how all fetuses should grow under optimal conditions. To construct the reference curves, all pregnancy complications, congenital anomalies and stillbirths were excluded, and a novel formula was used to calculate EFW, based only on HC and AC. Measurements were not revealed to the ultrasound operator, with the objective of avoiding corrections if extreme values were detected.[21]

Similar assumptions were taken to create the WHO fetal growth standards, including data collected from ten countries.[23] However, EFW was calculated using Hadlock's 1985 formula.[24] Due to the methodological differences in these studies their 10th and 90th percentiles vary substantially. For instance, at 28, 32 and 36 weeks, the 10th percentile of *'Intergrowth 21`* is 75, 164, and 208 g lower than those of the WHO, and the same tendency occurs with the 90th percentile. Curiously, the WHO study concluded that maternal characteristics such as height, weight and parity contribute to the differences in growth patterns observed between countries.

A different approach, known as customized Gestation-Related Optimal Weight (GROW) charts (www.gestation.net, Birmingham, United Kingdom) is proposed by Gardosi *et al.*[25] These charts consider variables known to affect fetal weight and growth, such as maternal height and weight, ethnic origin, parity and fetal sex. An online software is used to calculate gestational-age related EFW curves that are individually customized.[26,27] The model has been applied to several different datasets, allowing adaptations to the ethnic and nutritional characteristics of more than 25 countries.

A common criticism of customized growth charts is that nutritional status varies inside a country, namely between rural and urban areas, and that societies evolve due to changes in lifestyle and environment, as well as migratory fluxes. Anthropometric characteristics of the population will therefore evolve over time. The need to update reference ranges at regular intervals has been defended, [28,29] but some argue that this is not feasible. A major argument in favor of customized growth curves is that it allows the identification of SGA fetuses in obese mothers that were previously unrecognized when using population-based curves. It also avoids the exaggerated detection of SGA fetuses in thin and nulliparous women, thus avoiding unnecessary investigations and interventions.[30,31]

Use of customized growth charts is recommended by some scientific societies[32], but a recent systematic review failed to show their benefit over population-based charts in the identification of SGA neonates at risk of adverse outcomes.[33] Indeed it is difficult to demonstrate that growth curves improve the identification of pregnancies at increased risk of neonatal morbidity and mortality[34-36] or of adverse neurodevelopmental outcome.[37]

5. Assessment of fetal growth velocity

A single measurement of EFW can only indicate current size. Longitudinal evaluation is necessary to evaluate fetal growth, and to define a growth trajectory. Detection of an abnormal growth trajectory seems intuitively to be a better evaluator of a fetus failing to achieve its growth potential, the concept behind the definition of FGR. Both population-based and customized growth curves have been assumed to represent expected trajectories of normally growing fetuses.[38,39] Customization based on the initial EFW has also been proposed,[40] generating trajectories that represent individualized boundaries for a normally-growing fetus.[41] Fetal growth velocity can be evaluated by changes in EFW or in specific biometric indexes (AC or BPD).[42,43] The earlier the first examination is performed, the less likely it is to be biased by factors that impair fetal growth.[44]

Evidence has suggested that abnormal AC growth velocity is associated with perinatal morbidity in SGA fetuses.[38,45] In SGA fetuses, those with AC growth velocity in the lowest decile were at increased risk for neonatal morbidity (risk ratio [RR], 3.9; 95% confidence interval [CI], 1.9-8.1) compared with those showing normal AC growth velocity.[46]

A potential limitation of the growth velocity approach is the statistical phenomenon called *regression to the mean*, which implies that any variable with an extreme value in its first measurement will tend to be closer to the mean when evaluated repeatedly. Curiously, in low risk pregnancies, longitudinal assessment of fetal growth during the second and third trimesters has a lower predictive capacity for identifying SGA and late FGR than cross-sectional growth evaluation.[47] In contrast, for high-risk pregnancies, a better prediction of adverse perinatal outcomes was achieved with serial ultrasound measurements.[48,49] Because of these conflicting results[50] and issues related to the cost of this approach, there is insufficient evidence to recommend its wide clinical use, and one-time measurements remain standard practice.

Further studies are required to optimize the performance of serial measurement strategies, particularly to determine the optimal timing and interval between exams.

6. Fetal body proportions

Analysis of fetal body proportions is used to classify fetal growth as symmetric or asymmetric, in an attempt to distinguish between the different causes of FGR. When there is placental insufficiency, the brain-sparing effect causes AC to be the first biometric index affected by nutritional deficiency. Fetal body proportion models use ratios between AC and biometric indexes that are less affected by placental insufficiency, such as HC or FL. The concepts of symmetric and asymmetric fetal growth were widely disseminated in the last decades, namely as an aid to determine the etiology of FGR, but similarly to serial measurement strategies, there are conflicting results regarding their capacity to predict adverse perinatal outcomes.[51,52] Thus, the terms 'symmetrical' and 'asymmetrical' FGR should no longer be used, given that they do not provide additional information on etiology or prognosis.

7. Additional sonographic parameters

The biometric definition of SGA includes two different groups of fetuses: one that is in fact not achieving its genetic growth potential (true FGR) and another that is constitutionally small when compared with the reference population. Maternal history and symptoms, amniotic fluid assessment and Doppler velocimetry can provide additional information that may be used to identify fetuses at risk of adverse pregnancy outcome. Decreasing the cut-off value of EFW to < 3^{rd} centile reduces the number of constitutionally SGA fetuses and selects a higher risk population, associated with the worst neonatal outcomes.[53] Furthermore, the inclusion of functional data from umbilical, uterine, and middle cerebral arteries Doppler flowmetry contributes to the identification of true FGR fetuses.[54-56]

Umbilical artery (UA) Doppler primarily reflects early-onset placental insufficiency, and most experts agree that EFW < 10^{th} centile and abnormal UA Doppler provide the best criteria to identify early-onset FGR (diagnosis before 32 weeks).[57] However, UA neither reliably reflects placental insufficiency nor predicts adverse outcome in FGR detected beyond 32 weeks.[58] Middle cerebral artery (MCA) Doppler seems to be more valuable in the identification of late-onset FGR, as it has a stronger association with adverse perinatal and neurological outcomes.[59]

Cerebroplacental ratio (CPR), combining MCA and UA pulsatility index (PI), is an independent predictor of perinatal mortality, and seems to be more sensitive in detecting hypoxia than its individual components. Studies have shown that even in appropriately grown fetuses, an abnormal CPR is associated with a higher incidence of adverse perinatal outcomes.[60] The rationale behind this may be that these fetuses have a higher genetic growth potential and abnormal CPR reflects a deceleration in fetal growth.

Uterine artery (UtA) flowmetry reflects adequate trophoblastic invasion, an important step to guarantee adequate nutrient supply and gas exchange for the fetus. Although there is a positive association between abnormal uterine artery flow patterns and adverse outcomes such as preeclampsia and FGR, the predictive value of an isolated abnormal test is low, especially for late onset FGR.[57, 61-63]

Venous Doppler velocimetry does not have a role in the diagnosis of fetal growth anomalies, since changes appear late in the evolution of the disease. However, these measurements are useful for serial monitoring of fetal circulation, particularly in severe early onset FGR.[64,65]

Oligohydramnios is frequently seen in FGR, following redistribution of blood flow to vital organs at the expense of others, such as the kidney. This parameter can be evaluated by measuring the amniotic fluid index (AFI) or the single deepest vertical pocket (SDP). A randomized controlled trial comparing both methodologies found that AFI was associated with more frequent diagnoses of oligohydramnios and increased rates of labor induction, without improving perinatal outcomes. SDP may therefore be more valuable, particularly in the low risk population.[66,67] Nonetheless, there is limited evidence to support its use in screening of FGR, or as a predictor of adverse outcome.[68]

A sequential approach to identify and manage FGR is widely used in high-resource settings[69], where EFW is followed by Doppler evaluations to help differentiate between constitutional SGA and pathological fetal growth anomalies, and also to guide management and timing of interventions.

8. Third trimester ultrasound and late FGR

In accordance with recent guidelines from The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), screening for fetal growth abnormalities is an essential component of antenatal care, and fetal ultrasound plays a key role in assessment of these conditions.[70] It is important to differentiate between the concept of fetal size at a given time point and fetal growth, the latter being a dynamic process and the assessment of which requires at least two scans separated in time.

The indication for a third-trimester scan is based on local guidelines, and on the presence or absence of maternal or fetal conditions that are known to be associated with abnormal growth. In Portugal, in accordance with the guidelines from Direção Geral da Saúde (DGS) from 2015, FGR screening in low risk pregnancies is performed with an ultrasound for EFW at 30-33 weeks' gestation.[71] Nonetheless, data from ROUTE study, an open-label parallel randomized trial showed that FGR detection rate was superior at 36 *vs* 32 weeks' gestation (sensitivity, 38.8% *vs* 22.5%; $p = 0.006$). In cases of severe FGR, detection rate was also superior at 36 *vs* 32 weeks' gestation (61.4% *vs* 32.5%; $p = 0.008$).[72]

The difference between early and late FGR is based on gestational age at diagnosis: early onset as detected before 32 weeks' gestation and late onset as detected after 32 weeks' gestation.[57]

In our country, there is a lack of data on the prevalence and detection rate of FGR in low risk pregnancies. In order to improve FGR screening, it is important to study our population in order to test the strategies that have been internationally recommended as the most effective. To develop in the field and improve national guidelines, we consider that it is important to evaluate the reproducibility and accuracy of a late third trimester ultrasound for screening of FGR in low risk pregnancies.

9. Neurosonography in late FGR

Neurodevelopmental effects associated with fetal smallness are thought to be the result of changes in brain reorganization demonstrated by differences in regional volumes,[73] brain metabolism[74] and connectivity.[75] Several imaging biomarkers have been proposed as candidates to assess fetal neurodevelopment in small fetuses. For instance, corpus callosum (CC), brainstem and cerebellar measurements obtained by Magnetic Resonance (MR) were significantly altered in small fetuses and correlated with worse neurobehavioral performance.[76,77] Despite MR being the most widespread technique to assess CC and cortical development, neurosonography (NSG), which represents a cheaper and more readily available imaging technique, provides an excellent visualization of brain structures. MR studies have also shown different patterns of cortical development in small fetuses.[78,79] Cortical development is a continuous process involving several complex morphogenetic events that will ultimately lead to the maturation of brain fissures and sulci as present in term fetuses.[80] Indeed, cortical sulcation is considered a good marker of fetal brain maturation that could provide important information about the impact of prenatal insults on brain development. Whereas changes on specific brain structures have been evaluated in fetal smallness, the usefulness of fetal NSG to assess cortical development has been poorly explored.[81]

CHAPTER 2

AIMS OF THE THESIS

There is no consensus on the need for a third trimester ultrasound with the aim of screening for FGR in low risk pregnancies and so far, there is no evidence of any objective advantages on maternal and fetal outcomes. Nonetheless, a large study has demonstrated that for term low risk pregnancies, small- compared to appropriate-for-gestational-age babies have a significantly higher likelihood of composite neonatal morbidity, stillbirth, and neonatal mortality.[82] Death of a growth-restricted fetus is the second most common etiology of stillbirth. Moreover, a significant proportion of term stillbirths correspond to undiagnosed late FGR.[2,3,5] Sonographic fetal weight estimation during the third trimester in low risk pregnancies is an effective method for the diagnosis of FGR permitting a close surveillance and timely delivery.[46,83] However, the need for a routine ultrasound evaluation in low risk pregnancies and the best time to perform it remains controversial.

The overall aim of this thesis was to investigate the **best screening method for late FGR in low risk pregnancies**, by addressing three main questions:

1. When is the best time to perform third trimester ultrasound: 30-33 weeks *vs* 35-37 weeks?
We defined the following specific aims:
- to evaluate the prevalence of FGR in our population;
- to evaluate in a cross-sectional way the opinion of physicians regarding the importance of third trimester ultrasound and the best time to perform it;
- to evaluate the precision of the 35th-37th weeks' ultrasound and compare the accuracy of this ultrasound with that of the 30th-33rd weeks' ultrasound.

2. Is there an impact of a later third trimester ultrasound (35-37 weeks) on perinatal results?
We defined the following specific aim:
- to evaluate the impact of the 35th-37th weeks' *vs* the 30th-33rd weeks' ultrasound on the cesarean and instrumental deliveries' rate for non-reassuring fetal status.

3. Is there a role for neurosonography on the evaluation of late FGR?
We defined the following specific aims:
- to explore whether NSG can detect differences in grey and white matter in small fetuses;
- to evaluate if the pattern of changes is different when small fetuses are sub-classified into SGA or FGR.

CHAPTER 3

MATERIALS AND METHODS

1. Patient Recruitment and Outcomes

1.1. Part I

In order to establish the prevalence of FGR in our population of low risk pregnancies, a retrospective study was conducted at the Department of Obstetrics, Gynecology and Reproductive Medicine of Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte (HSM-CHULN), using the database of deliveries occurred during the year 2014.

Low risk pregnancies with term deliveries were selected. Newborns delivered at ≥ 37 weeks with birthweight < 10^{th} centile were considered SGA and with birthweight > 90^{th} centile were considered LGA. Appropriate for gestational age (AGA) corresponded to the term babies with 10^{th} centile ≤ birthweight ≤ 90^{th} centile. Birthweight centiles were calculated using reference curves published by Figueras *et al* in 2008.[29]

Medical records were revised in order to collect clinical data including maternal age, parity, gestational age at delivery, induction of labor, birthweight, third trimester ultrasound details, delivery route and admission of newborns to NICU.

Exclusion criteria were: no register of third trimester ultrasound in medical records, LGA, diabetes, hypertensive disorders of pregnancy, multiple gestation, autoimmune disease, previous pregnancy with FGR or preeclampsia, placental abnormalities, fetal malformations, chromosomal anomalies and TORCH infections.

According to national guidelines for surveillance of low risk pregnancies, a third trimester ultrasound for FGR screening was performed at 30-33 weeks. For every fetus, we collected the EFW in grams (g) and the correspondent centile for gestational age. EFW at 30-33 weeks' ultrasound < 10^{th} centile was considered antenatal detection of SGA. SGA babies with a 30^{th}-33^{rd} weeks' ultrasound ≥ 10^{th} centile were considered antenatal nondetected SGA.

The route of delivery (spontaneous vaginal, operative vaginal or cesarean delivery) and indications for cesarean and operative vaginal deliveries were compared between the SGA (n=151) and AGA (n=1202). Non-reassuring fetal status was defined by the interpretation of continuous cardiotocography (CTG), using the American College of Obstetricians and Gynecologists (ACOG) classification.[84]

1.2 Part II

In order to evaluate the intra and inter-observer reproducibility of third trimester ultrasound fetal biometric measurements at 35-37 weeks, a prospective study was conducted at HSM-CHULN. Patients were included if they had a single fetus pregnancy and if they accepted being submitted to three ultrasound evaluations on the same day at 35-37 weeks' gestation. Clinical data was collected: age, parity, body mass index (BMI) and maternal waist circumference (MWC) in cm. BMI was calculated with maternal height and weight measured at the beginning of pregnancy. MWC was measured to the nearest 1 cm at the midpoint between the lower ribs and the pelvic bone using a flexible tape.

We only included patients that had pregnancy dating based on a first trimester CRL measurement. All patients had to sign an informed consent before enrollment.
With this study, we also compared the reproducibility of third trimester ultrasound fetal biometric measurements in pregnant women with normal weight *vs* obese/excess weight.

1.3 Part III

In order to assess the opinion of Portuguese GOs and GPs on third trimester FGR screening, we have conducted a prospective cohort study based on application of surveys. Questionnaires were sent by e-mail to physicians and they filled them online. A second reminder e-mail was sent 7 days later. Questionnaires were announced by social media such as medical groups on Facebook. Recruitment was also done personally at scientific meetings. The questionnaires were completely anonymous.

In accordance to national statistics, there were 1772 GOs and 7149 GPs registered in Portugal as of 2018. All that have access to e-mail and/or attend scientific meetings were eligible to fill the survey.

The survey included questions about physician's demographics, training and practice characteristics. Responses were therefore assumed to refer to a respondent's self-reported current practices about the screening of FGR, offering a cross-sectional view.
Primary outcome was to compare the proportion of GOs that considered the need of a third trimester ultrasound (EFW) for FGR screening in low risk pregnancies and the best time to perform it with the corresponding proportion of GPs.

Secondary outcomes included: 1. to compare the opinion of GOs and GPs regarding the accuracy of symphysis-uterine fundus distance (SFD) for the screening of FGR in low risk pregnancies; 2. to compare the opinion of the two groups on the impact of a routine third trimester ultrasound on cesarean delivery rate for fetal distress and on the number of newborns admitted to the NICU.

We performed subgroup analysis of the endpoints described above based on current weekly activity (surveillance of low risk pregnancy and/or performing obstetric ultrasound). With this analysis, we expected to evaluate if there were any knowledge differences of physicians who regularly deal with the diagnosis, management and consequences of FGR in low risk pregnancies compared with those who do not have this current practice. All this data was included in preliminary questions at the beginning of the survey. It was made in a multiple-choice format and took less than 5 minutes to complete.

1.4 Part IV

We conducted a prospective randomized controlled trial in order to compare the accuracy of screening for late FGR between 30-33 weeks' and 35-37 weeks' third trimester ultrasound. The population included in this study corresponded to the low risk pregnant women with surveillance at the prenatal Consultation or referred by the primary care units to HSM-CHULN. The screening method for FGR currently used in low risk pregnancies is the measurement of the SFD at all visits from 24 weeks and a third trimester ultrasound scheduled for 30-33 weeks' gestation.

According to national guidelines, routine ultrasound scans were performed at 11 + 0 to 13 + 6 weeks' gestation for pregnancy dating, based on CRL, screening for congenital anomalies was performed at 20 + 0 to 22 + 6 weeks' gestation and screening of abnormal fetal growth at 30 + 0 to 32 + 6 weeks' gestation.[71]
After routine third trimester scanning, women meeting the following inclusion criteria were eligible to participate in the study: 1) viable singleton non-anomalous fetus; 2) pregnancy dating by ultrasound performed at 11 + 0 to 13 + 6 weeks' gestation; 3) maternal age at recruitment ≥ 18 years; 4) absence of medical history of diabetes, autoimmune or renal diseases, hypertensive disorders, fetal growth restriction or stillbirth.

The patients who agreed to participate in the study, after signing an informed consent, were randomized into 2 groups (with and without an additional ultrasound evaluation at 35-37 weeks). The randomization was done through computer software. Randomization sequences were generated in blocks of 100 participants to assure balanced distribution within study arms, in a 1:1 allocation ratio. It was not possible to blind participants, obstetricians or outcome assessors of the study group. Pregnant women were enrolled between July 2015 and May 2019.

Clinical data such as: maternal age, ethnicity, parity, height, weight, BMI at the beginning of pregnancy, education and smoking habits was collected at time of enrollment. Clinical evaluation included measurement of SFD. SFD was measured in cm with a tape with the numbers facing the maternal skin. The woman lied in a supine position and SFD corresponded to the longitudinal distance from the top of the uterine fundus to the upper border of the pubic symphysis.

Obstetric and neonatal outcomes such as: gestational age at delivery, type of labor (spontaneous or induced and respective indication), type of delivery (spontaneous vaginal, operative vaginal, antepartum or intrapartum cesarean section), indication for operative vaginal or cesarean delivery, CTG anomalies, gender, birthweight, birthweight centile, evidence of meconium staining of amniotic fluid, Apgar score, admission to NICU and perinatal mortality, were registered prospectively after delivery by revising medical records.

1.5 Part V

In order to assess the role of NSG on the evaluation of late FGR, a prospective cohort study was conducted at BCNatal (Hospital Clínic and Hospital Sant Joan de Déu) in Barcelona from January 2014 to June 2017.

The study population comprised singleton pregnancies classified into AGA and late onset small fetuses defined as a birthweight below the 10th centile according to local standards and confirmed after birth.[29] Small fetuses were further subdivided into late onset SGA (birthweight 3rd-9th centile, normal fetal and placental Doppler and diagnosis established later than 32nd weeks' gestation) or late onset FGR (birthweight below 3rd centile and/or CPR below 5th centile and/or UtA mean PI above 95th centile and diagnosis established later than 32 weeks' gestation). Uncomplicated term gestations with a birthweight above the 10th centile were included as controls. In all pregnancies, gestational age was calculated based on CRL measurement on first-trimester ultrasound and weight centiles were calculated using local reference curves.[29] Pregnancies with congenital malformations, chromosomal abnormalities or fetal infection were excluded. The following data were recorded upon enrollment: maternal age, ethnicity, BMI, parity, smoking status and obstetric history data such as in vitro fertilization (IVF), preeclampsia (PE) or gestational diabetes. At delivery, gestational age, gender, birthweight, birthweight centile, Apgar score, umbilical artery pH and route of delivery were collected.

2. Ultrasound measurements

All measurements performed during the third trimester ultrasound were obtained at the appropriate levels described elsewhere, with the fetal structure of interest filling at least 30% of the monitor and were recorded in mm.[85,86] BDP and HC were taken from axial images of the fetal brain at the transthalamic plane, with an angle of insonation as close as possible to 90°. Evidence has shown that, particularly in late gestation, this section plane is easier to identify and allows for more reproducible measurements than the transventricular plane.[87] The head had to be oval in shape, symmetrical and centrally positioned. The midline echo (representing the falx cerebri) had to be broken anteriorly, at a third of its length, by the cavum septi pellucidi. BPD was measured by outer-to-inner caliper placement at the widest part of the skull. Reproducibility studies have demonstrated that both outside to outside and outside to inside measurements are equivalent.[87] We adopted the outer to inner technique in order to avoid artifacts generated by the distal echo of the calvarium. The measurement of AC was taken in a cross-sectional view of the fetal abdomen as close as possible to circular, at the level of the bifurcation of the main portal vein into left and right branches and with the stomach visible. Both HC and AC were measured using the ellipse facility on the outer border of the skull and of the abdomen, respectively. No manual tracing was used. FL was measured using a longitudinal view of the fetal thigh closest to the probe and with the femur as close as possible to the horizontal plane. Measurement was performed with the full length of the bone visible by including only the femoral diaphysis length, excluding the hypoechogenic cartilaginous structures at either end of femur.

For the reproducibility study (Part III), we compared fetal biometric measurements instead of the EFW since this is estimated by applying one of many formulae to the individual parameters and all formulae have a specific margin of error of at least +/- 15%. Each measurement was evaluated twice by the first observer and a third time by a second observer that was blinded to the first observer's measurements. Five sonographers participated in the study: three residents in the second half of their residency program and two consultants with less than 5 years of experience. The ultrasound equipment package used was a GE Voluson E8 (GE Healthcare Ultrasound, 9900 Innovation Drive Wauwatosa, WI, USA 53226) with 3.5-MHz transducer.

For the randomized trial (Part IV), the ultrasound performed for the study group (at 35-37 weeks), included biometric parameters of the fetus: BPD, HC, AC and FL. Based on these measurements, the computer system (Astraia®) provided the EFW and respective percentile according to the Hadlock formula[24] and Yudkin curves.[88] Amniotic fluid was also measured by SDP. Functional evaluation included: Doppler of the UA, MCA and UtA. The respective PI and CPR were registered. All Doppler evaluations were performed automatically in the absence of somatic and respiratory fetal movements, under transitory maternal apnea, with the lowest insonation angle possible and at least 3 successive complexes were evaluated for each measurement.

For Part V study, detailed NSG was performed in both cases and controls using a transabdominal and transvaginal approach during the third trimester of pregnancy. In small fetuses, NSG exam was performed 10±4 days after the initial diagnosis. Controls matching the gestational age of small fetuses at NSG, were recruited from the general population. Fetal brain exams were performed using a standardized approach based on the ISUOG guidelines for fetal brain assessment.[89,90] Patients with insufficient image quality for delineation of measurements were excluded.

Imaging post-processing and measurements were performed using the Alma Workstation software® by two examiners blinded to the study group. Systematic evaluation of cortical development was performed by measuring fissures according to the description of Alonso et al.[91] and to previous studies of cortical development.[79,92]

Insula depth was measured in the transthalamic axial plane drawing a perpendicular line from the midline towards the most external border of the insular cortex. Sylvian fissure depth was measured continuing the perpendicular line from the insular cortex towards the inner parietal bone. Parieto-occipital fissure depth was evaluated in a slightly cranial plane from the transventricular plane, where the full depth and triangle shape of the fissure was visualized. The depth was measured drawing a perpendicular line from midline to the apex of the triangle which was pointing to the periphery.[91] CC length and vermis height were measured in a midsagittal plane that accomplished strict criteria defined as: the identification of the cavum septi pellucidi, thalamus, midbrain, cerebellar vermis and cisterna magna.[93] CC length was measured from the most anterior part of the genu to the most posterior part of the splenium tracing a straight rostrocaudal line between the two points, known as the outer-to-outer CC length.[94] Vermis height or craniocaudal length was measured as the maximal distance between the most cranial part of the culmen and the most caudal part of the uvula.[95] In order to correct the condition of a smaller head size influencing the size of brain structures in small fetuses, insula depth, sylvian fissure depth, parieto-occipital fissure and vermis height were corrected by BPD and CC length was corrected by cephalic index (CIX) and all measurements were expressed as ratios. BPD and Occipitofrontal diameter (OFD) were measured in the transthalamic plane following ISUOG guidelines.[89] CIX was calculated using BPD and OFD by applying the formula CIX = BPD/OFD*100.

3. Definition of FGR and monitoring

FGR was defined according to the ACOG as a fetus with an EFW below the 10th percentile and SGA as a newborn with a birthweight below the 10th percentile.[11]

Prospective studies only included pregnancies with gestational age calculated based on CRL measurement on first-trimester ultrasound and with routine mid-trimester ultrasound scan that ruled out congenital anomalies and early FGR.

In order to stratify FGR, as mentioned in the ultrasound measurements section, during each ultrasound, we collected other data such as Doppler parameters (UA, MCA, UtA, CPR, SDP of amniotic fluid).

For the randomized trial's (Part IV) control group (women with a routine ultrasound at 30-33 weeks), local guidelines for follow up included serial evaluation of the SFD at scheduled appointments at 35, 38, 40 and 41 weeks. If this distance was less than 31 cm at 35 weeks or less than 34 cm at 38, 40 or 41 weeks, the clinical suspicion of FGR mandated an ultrasound evaluation as described above. If no deviation of SFD was found, induction of labor was scheduled at 41 weeks and delivery route was decided by obstetric criteria.

In accordance with our Department's protocol for the surveillance of FGR, for the study group with ultrasound diagnosis of FGR, the management was as described below:
- FGR with EFW < 10^{th} centile and normal Doppler - Doppler re-evaluation after one week and EFW + Doppler after two weeks. If Doppler is normal and the fetus remains on the same growth curve, ultrasound controls are performed every two weeks and delivery is scheduled at 39 weeks.
- FGR with EFW or AC < 3^{rd} centile or EFW < 10^{th} centile + UA IP > 95^{th} centile: weekly Doppler and CTG. EFW every two weeks. If no additional Doppler anomalies in all evaluations, delivery is scheduled at 37 weeks.
- FGR with CPR < 5^{th} centile or MCA PI < 5^{th} centile; Doppler evaluation three times per week; CTG every 8 hours; EFW every two weeks. If no additional Doppler anomalies in all evaluations, delivery is scheduled at 37 weeks.
- FGR with absent or reversed end diastolic flow in UA are indications for delivery at the gestational age of the ultrasound evaluation in the study group.

For all groups, in the presence of Doppler anomalies, these should be confirmed in 6-12 hours. Delivery route was decided according to obstetric criteria.

For both groups, antenatal detection of FGR was confirmed after the birth (about five weeks after recruitment), by comparing antenatal EFW centiles of both ultrasounds (30-33 and 35-37 weeks) with birthweight centiles.

4. Ethical issues

Part I-II and IV studies of this thesis were approved by the Lisbon Academic Medical Center Ethics Committee (reference number 387/13). Written informed consent was obtained from each woman before enrollment in the studies.

For Part III study, we had the approval of National Scientific Societies in order to distribute the questionnaires. When physicians register on scientific societies, they give permission to receive e-mails and no further ethics committee or informed consent is required for this type of study.

Part V study was developed in BCN Hospital Clinic Barcelona and had the approval of the Ethics Committee of that center (review board 2014/7154) and all patients gave written informed consent.

5. Statistical analysis

Normal distributions were assessed using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation (SD), median (interquartile range (IQR)) or number of subjects (%). Statistical analyses were performed using STATA 14.1 (Statacorp, College Station, Texas, US) and R-3.3.2.

Chi-square test or Fisher's exact test and analysis of variance (ANOVA) or Kruskal Wallis (non-parametric) test were used to compare categorical and continuous variables among groups, respectively. Student's t-test or Mann–Whitney U test were used to compare two groups.

For Part II study, the consensus between and among observers was analyzed using Pearson correlation coefficient (inter and intra-CC, respectively) and the Crohnbach´s α reliability coefficient (α-RC). A value > 0.75 was considered a reliable consensus for the intra-CC, inter-CC and α-RC. Considering that two measurements made by the same sonographer or by two different sonographers are all the closest to a real measure (not observed), α-RC is a coefficient that measures the reliability of the measurement. Since the three evaluations of the same parameter for the same woman were made at different time points but very close to each other, the closer the measurements are to each other, the more reliable the methods. This reliability is evaluated by the α-RC. In this study, we compared intra and inter-observer measurements within subgroups of maternal weight – women with normal weight (BMI < 25 Kg/m^2) and overweight women (BMI ≥ 25 Kg/m^2) with paired sample t-test. We also compared intra and inter-observer measurements within subgroups of maternal waist circumference - MWC ≥ 104 cm and MWC < 104 cm. The Bland and Altman plots were created to determine agreement and bias between paired measurements by one observer and by two observers, respectively. If there is perfect agreement between the measurements, the difference between them should be zero. We considered high reproducibility if the mean difference was close to zero and with low dispersion around zero (95% of the points of the graph between the two limits).

For Part III study, for ordinal variables, we considered the following hypotheses to classify the agreement rate: null (0%), low (<10%), moderate (10-90%), high (>90%). As far as we know there is no study comparing the opinion of physicians regarding FGR screening. Since we had no data on which to base our expected difference between groups in order to estimate sample size, we decided to use the total of physicians included in this study that were registered at the National Medical Council. We may hypothesize that physicians are used to following national guidelines and that around 75% of GPs will consider that 30-33 weeks is the best time to perform third trimester ultrasound, leaving about 25% who would select 35-37 weeks. Recent evidence has been highly debated in scientific meetings of GOs and we may consider that these physicians might be more aware of this with a higher proportion selecting 35-37 weeks. In our baseline population, we have a ratio of GPs/GOs of 4.03 (7149/1772). Considering a response rate of 20%, we would include 1430 GPs (N1 = 7149 x 0.20) and 354 GOs (N2 = 1772 x 0.20), with N1/N2 = 4.03. Given that around 25% of GPs would choose 35-37 weeks, for a total sample size of 1784 (N1+N2), with a significance α level of 0.05 and 80% power, we would expect to be able to detect a difference of 8% between the proportions of GPs and GOs that would select 35-37 weeks as the best time to perform the ultrasound.

For Part IV randomized trial, according to our retrospective analysis (Part I), the antenatal ultrasound detection rate of FGR at 30-33 weeks is 20.5% for low risk pregnancies. Aiming to increase the detection rate by at least 7% with an ultrasound at 35-37 weeks (study group), the investigators would require a total sample of 1200 women (600 in each group - control with ultrasound at 30-33 weeks and study with an additional ultrasound at 35-37 weeks), with 80% power and a significance α level of 0.05. Analysis was primarily based on originally-assigned groups (intention-to-treat). A secondary per-protocol analysis was performed by excluding the cases that missed the scheduled ultrasound from the study group and the cases that were submitted to an additional ultrasound after enrolment from the control group.

For Part V, linear polynomial orthogonal contrast tests were also used to test the hypothesis of a linear association across severity groups (controls-SGA-FGR). Following standard methodology, data were adjusted for confounding factors as fetal gender and gestational age at NSG by linear regression analysis.

For all comparisons, two-sided p-values < 0.05 were considered statistically significant.

CHAPTER 4

RESULTS

1. Part I: Small-for-gestational-age babies of low-risk term pregnancies: does antenatal detection matter?

1.1 Results

During the year 2014, there were 2193 deliveries at HSM-CHULN, with 539 cesarean deliveries (25%) and 620 operative vaginal deliveries (28%).

In total, 1429 (65%) corresponded to term low risk pregnancies. Within these, there were 11% (151/1429) SGA babies, 5% (76/1429) LGA and 84% (1202/1429) AGA babies.

Cesarean delivery rate among term low risk pregnancies was 18% (256/1429). We excluded the 76 cases of LGA from the analysis.

Clinical characteristics of women who had SGA babies (n =151) and of women with AGA babies (n=1202) are presented in Table 1. In both groups the majority of women were nulliparous. Nonetheless, the AGA group had a statistically significant higher proportion of multiparous than the SGA group (44% *vs* 30%, $p = 0.01$). However, the proportion of multiparous with previous cesarean delivery was not statistically different between the two groups. SGA group had a statistically significant lower mean gestational age at birth than AGA (39.1 *vs* 39.6 weeks, $p < 0.001$). Induction of labor had been more frequently decided in the SGA group than in the AGA. In the former group a large proportion of inductions of labor were performed because of ultrasound antenatal diagnosis of SGA (38%) whereas in the AGA group, 96% had an induction indicated by gestational age or term prelabor rupture of membranes.

SGA babies were associated with a higher rate of cesarean deliveries for non-reassuring fetal status [18/151 (12%) *vs* 8/1202 (1%), $p < 0.001$], higher rate of operative vaginal deliveries for non-reassuring fetal status [24/151 (16%) *vs* 12/1202 (1%), $p < 0.001$] and higher rate of admissions to the NICU [16/151 (11%) *vs* 18/1202 (1%), $p < 0.001$] compared to AGA (Table 1).

Table 1: Comparison of demographic characteristics and obstetric outcomes between women with small babies and women with adequate weight babies

Variables	Small for gestational age (n=151)	Adequate weight for gestational age (n=1202)	*p* value
Maternal age (y) (mean ± SD)	29.7 ± 6.3	30.2 ± 6.0	0.29
Parity (n [%])			0.01
Nulliparous	106 (70)	668 (56)	
Multiparous	45 (30)	534 (44)	
Previous cesarean delivery (n [%])	16 (11)	127 (11)	0.99
Gestational age at delivery (wk) (mean ± SD)	39.1 ± 1.4	39.6 ± 11	<0.001
Induction of labor n (%)	64 (42)	285 (24)	<0.001
Operative vaginal rate (n [%])	40 (26)	368 (31)	0.30
Operative vaginal for non-reassuring fetal status (n [%])	24 (16)	12 (1)	<0.001
Cesarean section rate (n [%])	35 (23)	218 (18)	0.13
Cesarean section for non-reassuring fetal status (n [%])	18 (12)	8 (1)	<0.001
Admission to neonatal intensive care unit (n [%])	16 (11)	18 (1)	<0.001

Abbreviations: y, years; SD, standard deviation; wk, weeks.

Within SGA group (n = 151) 21% of babies (31/151) had been detected antepartum by ultrasound. Antenatal detection was associated with lower gestational age at delivery (37.8 *vs* 39.5 weeks, p < 0.001), more inductions of labor (24/31 *vs* 7/120, p < 0.001), lower mean birthweight (2301 *vs* 2594g, p<0.001) and lower rates of operative deliveries for non-reassuring fetal status (3/31 *vs* 39/120, p = 0.01) compared to undetected SGA (Table 2).

Table 2: Comparison of demographic characteristics and obstetric outcomes between antepartum detected *vs* nondetected small for gestational age babies

	Antepartum detected SGA (n=31)	Antepartum nondetected SGA (n=120)	*p* value
Maternal age (y) (mean ± SD)	29.2 ± 6.4	29.8 ± 6.3	0.69
Parity (n [%])			0.15
Nulliparous	25 (81)	81 (67)	
Multiparous	6 (19)	39 (33)	
Gestational age at delivery (wk) (mean ± SD)	37.8 ± 0.9	39.5 ± 1.2	<0.001
Induction of labor (n [%])	24 (77)	7 (6)	<0.001
Birthweight (g) (mean ± SD)	2301 ± 247	2594 ± 213	<0.001
Operative vaginal rate (n [%])	5 (16)	26 (22)	0.14
Operative vaginal for non-reassuring fetal status (n [%])	2 (6)	22 (18)	0.11
Cesarean section rate (n [%])	8 (26)	23 (19)	0.70
Cesarean section for non-reassuring fetal status (n [%])	1 (3)	17 (14)	0.12
Operative delivery for non-reassuring fetal status (n [%])	3 (10)	39 (33)	0.01
Admission to neonatal intensive care unit (n [%])	5 (16)	26 (22)	0.26

Abbreviations: SGA, small for gestational age; y, years; SD, standard deviation; wk, weeks; g, grams.

1.2. Discussion

SGA were associated with higher cesarean and operative vaginal deliveries for non-reassuring fetal status and higher rate of admissions to the NICU compared to AGA. This higher rate of obstetric intervention for non-reassuring fetal status in SGA group may be due to the fact that these fetuses have a lower placental reserve near term, making them unable to overcome the demands of labor. The higher rate of admissions to the NICU for SGA than AGA may also be an evidence of the lower placental reserve of these fetuses.

Since this retrospective study described the outcomes of term low risk pregnancies in one year we could not address less frequent outcomes such as the risk of stillbirth and neonatal mortality. Nonetheless, Mendez-Figueroa *et al* published a multicentric analysis of 50,011 uncomplicated term pregnancies and they concluded that SGA compared to AGA babies had a significantly higher likelihood of composite neonatal morbidity, stillbirth, and neonatal mortality.[82,96]

We performed a secondary analysis of the 151 cases of SGA and compared antenatally detected with antenatally undetected SGA. Using the criterion described above we verified a detection rate of SGA of 21%. In our sample of 151 SGA babies from low risk pregnancies the antenatally detected group had lower gestational age at delivery and lower birthweight compared to nondetected, which was probably due to more inductions of labor decided because of the diagnosis of SGA. Our data is consistent with the literature and though we were not able to evaluate neonatal outcomes other than admission to NICU, a similar study has concluded that despite antenatally detected SGA babies having lower birthweights and lower gestational age at birth than undetected SGA, they had significantly lower mortality (6.4 *vs* 12.6%) than undetected SGA without a parallel increase in severe 2-year neurodevelopmental, clinical, or growth morbidity.[97]

We found a statistically significant association between antenatally undetected SGA and higher operative deliveries for non-reassuring fetal status. This reinforces the hypothesis that antenatal detection of SGA permits a term induction of labor and timely delivery preventing SGA fetuses from being exposed to a post term pregnancy that might be too demanding for their placental reserve.

The retrospective design of our study did not allow collecting data on functional parameters evaluated at the third trimester ultrasound. A term SGA was considered as a newborn with birthweight < 10^{th} centile. Birthweight centiles were calculated using reference curves for Spanish population given the ethnic similarity to our population and the lack of local curves at the beginning of this thesis. Antenatal detection of these SGA babies was considered when EFW was < 10^{th} centile. In accordance to the ACOG this is the definition of FGR.[11] Nonetheless this definition includes two different groups of fetuses: one group that is not achieving its genetic potential of growth (true FGR) and another group of fetuses that are only constitutionally small for gestational age. Concomitant data suggests that additional ultrasound parameters could help to distinguish these two types of fetuses. For instance, decreasing the EFW percentile cut off to < 3^{rd} centile could prevent inclusion of a large number of constitutionally small for gestational age since several studies have reinforced that the fetuses with EFW < 3^{rd} centile are the ones with the worst neonatal outcomes.[53] In our series, birthweight was also inversely associated with admission to NICU and with operative deliveries for non-reassuring fetal status.

In fetuses with 3^{rd} centile < EFW < 10^{th} centile, inclusion of functional data, in particular, UA PI and MCA PI would contribute to identify true FGR.[54-56] CPR is an independent predictor of perinatal mortality. Studies have shown that even for AGA fetuses, an abnormal CPR is associated with higher incidence of adverse outcomes.[60] It is hypothesized that these fetuses had a higher genetic growth potential and CPR may demonstrate this growth deceleration.

We acknowledge the design of the study as a major limitation since it is a retrospective study based on revision of medical records and we cannot disclose the possibility of misclassification of the outcomes and uncertain validity of the data obtained from the medical records. Nevertheless, we tried to compare demographic characteristics between groups, especially potential confounders associated with higher rate of cesarean and operative vaginal deliveries for non-reassuring fetal status on SGA compared to AGA. However, there are other variables that were not systematically registered in the medical records such as BMI, smoking, social and economic status and those could have been potential confounders as well.

In conclusion, in our series of term low risk pregnancies, SGA babies had higher operative deliveries for non-reassuring fetal status than AGA and were also more frequently admitted to NICU.

2. Part II: Impact of maternal weight in intraobserver and interobserver reproducibility of fetal biometry in third trimester ultrasound

2.1. Results

This was a prospective observational cohort study conducted at a tertiary hospital, between January 2015 and July 2016. We included 197 women, 18 with low weight (9%), 115 with normal weight (58%), 44 with excess weight (22%) and 20 obese (10%). Demographic characteristics are represented in Table 3.

Table 3: Demographic characteristics (n = 197)

Variables	Value
Maternal age (y) (mean ± SD)	29.7 ± 5.5
Parity (n [%])	
Nulliparous	121 (61.4)
Multiparous	76 (38.6)
BMI at beginning of pregnancy (Kg/m^2) (mean ± SD)	23.8 ± 4.5
BMI group	
Low weight (< 18.5 Kg/m^2)	18 (9.1)
Normal weight (≥ 18.5 and < 25 Kg/m^2)	115 (58.4)
Excess weight (≥ 25 and < 30 Kg/m^2)	44 (22.3)
Obese (≥ 30 Kg/m^2)	20 (10.2)
Maternal weight gain at ultrasonography (Kg) (mean ± SD)[a]	11.4 ± 4.9
Maternal waist circumference at ultrasonography (cm) (mean ± SD)	104.1 ± 8.5
Pregnancy duration at ultrasonography (wk) (mean)	36

Abbreviations: y, years; SD, standard deviation; BMI, body mass index (calculated as weight in kilograms divided by the square of height in metres); wk, weeks.

[a] Compared with pre-pregnancy weight.

For all women, all measurements were obtained in accordance with the guideline indications described in Materials and Methods section. No incomplete ultrasound evaluation was registered, corresponding to a total of 591 ultrasound evaluations performed.

Both groups of BMI pregnant women registered very high intra- and inter-observer correlation coefficients and α-RC for all four biometric parameters. All of them were above 0.90 for both groups, except for HC inter-observer coefficients (inter-CC 0.87 for BMI < 25 Kg/m^2 and inter-CC 0.89 for BMI ≥ 25 Kg/m^2), both with α-RC > 0.90 (Table 4).

Table 4: Intra- and inter-observer correlation and reliability of fetal ultrasonography biometric measurements, stratified by early-pregnancy BMI

Parameter	Intra-observer reliability		Inter-observer reliability	
	Pearson correlation coefficient (95% CI)	Cronbach α reliability coefficient	Pearson correlation coefficient (95% CI)	Cronbach α reliability coefficient
BMI < 25				
BPD	0.94 (0.92-0.96)	0.97	0.94 (0.92-0.96)	0.97
HC	0.91 (0.88-0.94)	0.95	0.87 (0.82-0.90)	0.93
AC	0.96 (0.95-0.97)	0.98	0.97 (0.95-0.98)	0.98
FL	0.92 (0.89-0.92)	0.96	0.91 (0.87-0.93)	0.95
BMI ≥ 25				
BPD	0.94 (0.91-0.97)	0.97	0.95 (0.91-0.97)	0.97
HC	0.93 (0.89-0.96)	0.96	0.89 (0.82-0.93)	0.94
AC	0.96 (0.93-0.98)	0.98	0.97 (0.95-0.98)	0.98
FL	0.94 (0.90-0.96)	0.97	0.92 (0.87-0.95)	0.96

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

Unlike BMI, MWC reference cut off is not defined for pregnant women. From the analysis of our cohort, mean and median values for MWC were 104.1 and 104 cm, respectively. We used the value 104 cm as our cut off and we stratified our sample in two groups: higher MWC ≥ 104 cm and lower MWC < 104 cm. Similarly to what we have seen for BMI, for MWC stratification we verified that there was slightly less agreement in the correlation coefficients of head measurements than for abdomen or femur measurements. Nevertheless, all α-RC were > 0.90 (Table 5).

Table 5: Intra- and inter-observer correlation and reliability of fetal ultrasonography biometric measurements, stratified by maternal waist circumference at ultrasonography

Parameter	Intra-observer reliability		Inter-observer reliability	
	Pearson correlation coefficient (95% CI)	Cronbach α reliability coefficient	Pearson correlation coefficient (95% CI)	Cronbach α reliability coefficient
MWC < 104 cm				
BPD	0.94 (0.91-0.96)	0.97	0.93 (0.90-0.95)	0.96
HC	0.89 (0.84-0.93)	0.94	0.88 (0.82-0.92)	0.93
AC	0.94 (0.92-0.96)	0.97	0.95 (0.93-0.97)	0.98
FL	0.93 (0.90-0.95)	0.97	0.90 (0.86-0.94)	0.95
MWC ≥ 104 cm				
BPD	0.94 (0.91-0.96)	0.97	0.95 (0.92-0.96)	0.97
HC	0.93 (0.90-0.95)	0.97	0.85 (0.78-0.90)	0.92
AC	0.97 (0.95-0.98)	0.98	0.97 (0.96-0.989)	0.99
FL	0.92 (0.89-0.95)	0.97	0.92 (0.88-0.94)	0.96

Abbreviations: CI, confidence interval; MWC, maternal waist circumference; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

Furthermore, intra and inter-observer fetal measurement differences for all groups of pregnant women (according to BMI and according to MWC) were not considered statistically significant (Table 6).

Table 6: Mean differences in intra-observer and inter-observer biometric measurements

Comparison groups	Comparison of mean differences (*p* value)[a]			
	BPD	HC	AC	FL
Intra-observer difference for patients with BMI < 25	0.10	0.23	0.89	0.11
Intra-observer difference for patients with BMI ≥ 25	0.82	0.96	0.48	0.65
Inter-observer difference for patients with BMI < 25	0.21	0.21	0.33	0.33
Inter-observer difference for patients with BMI ≥ 25	0.72	0.59	0.26	0.48
Intra-observer difference for patients with MWC < 104 cm	0.16	0.13	0.75	0.17
Intra-observer difference for patients with MWC ≥ 104 cm	0.45	0.81	0.28	0.38
Inter-observer difference for patients with MWC < 104 cm	0.25	0.77	0.37	0.12
Inter-observer difference for patients with MWC ≥ 104 cm	0.96	0.45	0.47	0.86

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BPD, biparietal diameter; HC, head circumference; FL, femur length; MWC, maternal waist circumference.

[a]Paired-sample *t* test

Figures 1 and 2 depict Bland and Altman plots for BPD, HC, AC and FL taken by the same and different observers for all patients included and stratified by group of BMI. For all parameters, we verified that all mean differences were close to zero and that 95% of the intra and inter-observer mean differences were within the dashed lines. This reinforces that intra and inter-observer fetal measurement differences were not statistically significant.

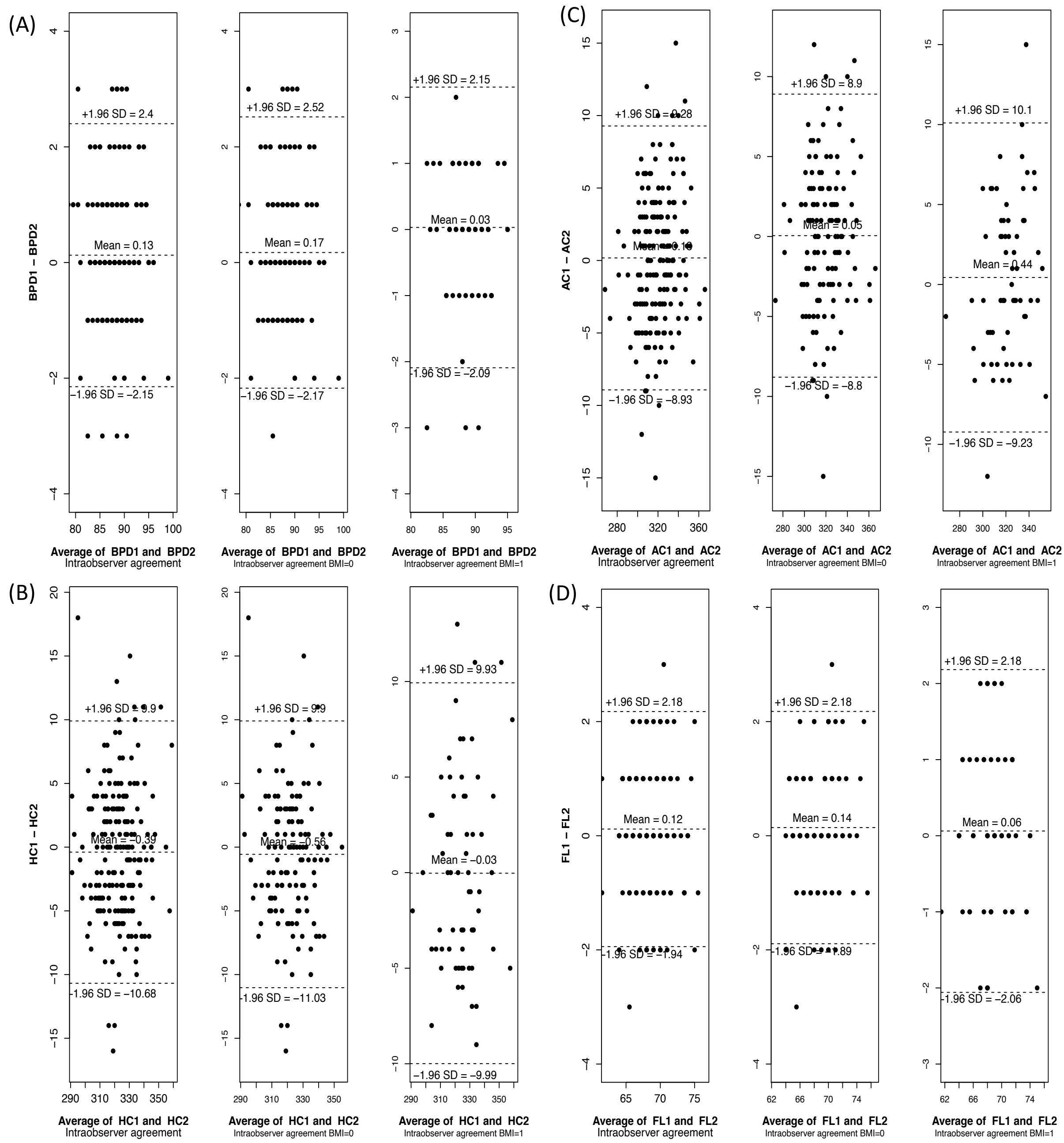

Figure 1: Bland-Altman plots of the mean difference (with 95% limits) in BPD (A), HC (B), AC (C), and FL (D) measurements performed by the same operator. BMI=0 indicates patients with BMI < 25, and BMI=1 indicates patients with BMI ≥ 25.

Abbreviations: BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; BMI, body mass index (weight in kilograms divided by the square of height in meters).

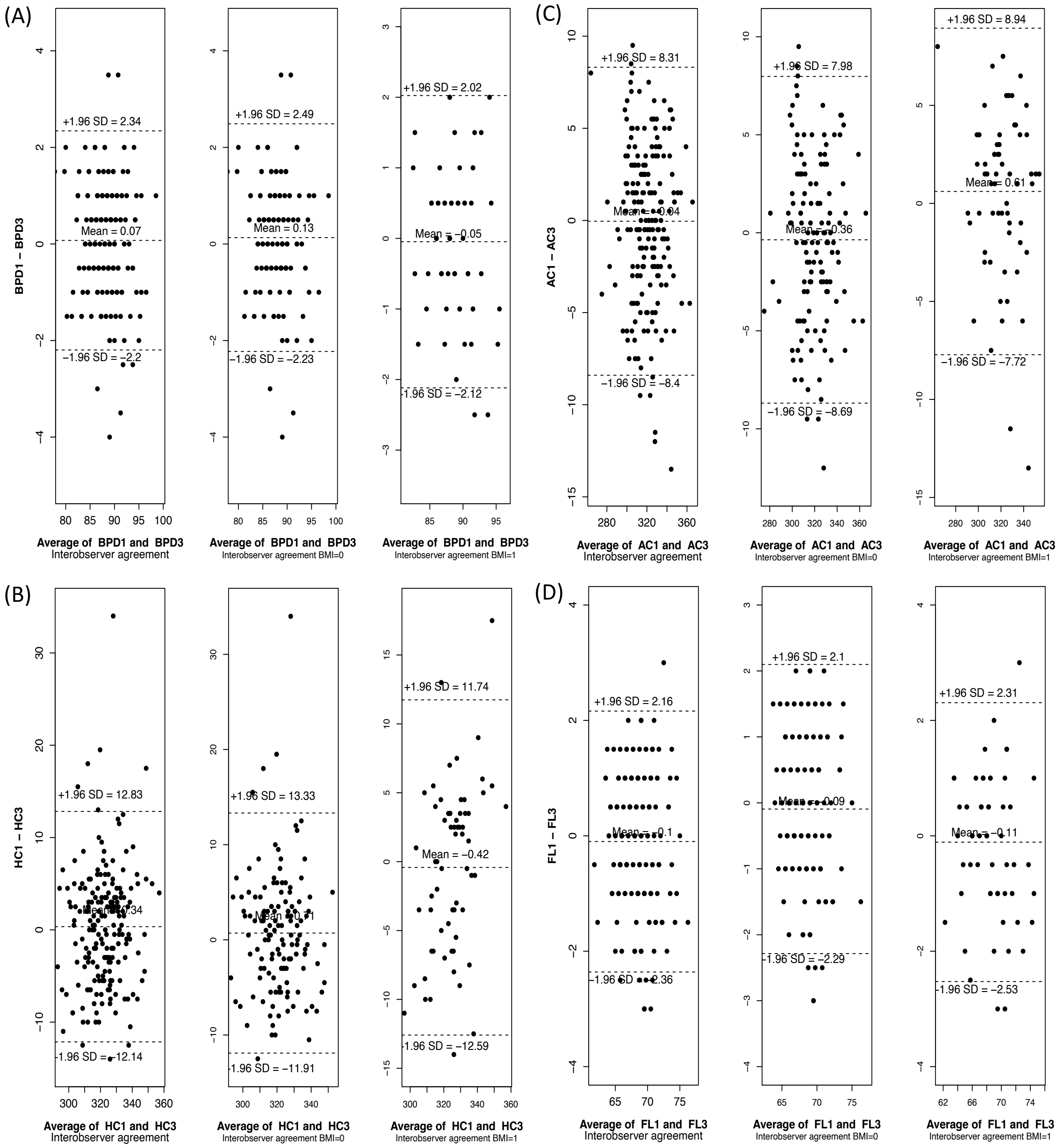

Figure 2: Bland-Altman plots of the mean difference (with 95% limits) in BPD (A), HC (B), AC (C), and FL (D) measurements performed by the two different operators. BMI=0 indicates patients with BMI < 25, and BMI=1 indicates patients with BMI ≥ 25.

Abbreviations: BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; BMI, body mass index (weight in kilograms divided by the square of height in meters).

2.2 Discussion

Considering the data that suggested a superior detection of FGR at 36 *vs* 32 weeks' gestation ultrasound,[72] our group decided to assess the intra- and inter-observer reproducibility of biometric measurements at 35-37 weeks. Moreover, since there is also controversy on the accuracy of EFW at the third trimester ultrasound of high BMI women compared to lower BMI women we assessed the reproducibility of the parameters within BMI groups to also validate the method for this population.

Although several studies have evaluated the mean error of EFW at third trimester ultrasound,[98-100] as far as we know this is the first study evaluating the reproducibility of fetal biometric ultrasound measurements in the third trimester in high BMI pregnant women compared to normal weight women. Studies published evaluated reproducibility of ultrasound in a wide range of gestational ages.[101] Authors have reported that ultrasound accuracy gradually deteriorates as the number of weeks of gestation increases and this deterioration is higher with increased BMI.[99,102] Our study has the advantage of restricting the analysis of reproducibility to a tight gestational age interval. At 35-37 weeks, we verified high intra and inter-sonographer measuring accuracy with reliability and correlation coefficients for almost all biometric parameters above 0.9, independent of maternal weight and abdominal circumference. We only found coefficients between 0.8-0.9 for head measurements which can be explained by some technical challenges of scanning late in the third trimester such as head lying low in the pelvis and less amniotic fluid. Both circumstances may make it more difficult to obtain perfect imaging planes of the head. Nonetheless correlation coefficients as high as those obtained still reinforce the high reliability of ultrasound measurements.

Studies have suggested that higher maternal abdominal wall thickness is associated with lower probability of completing the ultrasound evaluation in obese pregnant women and with poor image quality.[103] Absorption of ultrasound beams by subcutaneous fat makes scans more difficult.[104] MWC may be an indicator of higher abdominal wall thickness and fat. Recently, a study reported that MWC may be a predictor of failure of EWF defining as an optimal cut off value 105 cm with 70% sensitivity and 61% specificity.[105] Nonetheless we concluded that both groups of higher and lower MWC had high reproducibility of fetal biometric measurements.

In accordance with other studies that reported good accuracy of ultrasound performed by residents and inexperienced operators,[106] we also found high reliability of fetal measurements performed by non-experienced sonographers.

We acknowledge as a limitation of our study the fact that we included in the same group excess weight women and obese women. The number of women in the obese category was small which prevented us from analyzing more deeply the impact of obesity in ultrasound reproducibility. Ideally, with a larger sample size, we would have split them in two groups and by isolating obese women the power of our results would be increased. Nevertheless, our main aim was to test whether there was similar accuracy of fetal measurements in normal weight *vs* overweight women. We did not intend to evaluate the technical difficulty of performing the ultrasound evaluation in our cohort. In an attempt to do so, it would be interesting, as a future research line, to evaluate intra and inter-observer quality of the images obtained for both groups.

To conclude, in our sample, we demonstrated high intra and inter-observer reproducibility of third trimester ultrasound fetal biometric measurements, even for overweight women.

3. Part III: National-survey for evaluation of the best screening method of late fetal growth restriction in low risk pregnancy: a prospective study

3.1 Results

A total of 573 surveys were available for analysis, 298 corresponded to GOs and 275 to GPs, with a response rate of 17% and 4%, respectively. Demographic characteristics are described in Table 7.

Table 7: Demographic characteristics of GOs and GPs respondents

Variables	Gynecologists/ Obstetricians (n = 298)	General Practitioners (n = 275)	*p* value
Age (y) [median (IQR)]	34 (30;45)	32 (29;36)	< 0.001
Sex (n [%])			0.98
Female	257 (86.2)	237 (86.2)	
Male	41 (13.8)	38 (13.8)	
Position (n [%])			0.97
Resident	124 (41.6)	114 (41.5)	
Consultant	174 (58.4)	161 (58.5)	
Performs weekly surveillance of low risk pregnancy (n [%])	220 (73.8)	251 (91.3)	< 0.001
Performs weekly obstetric ultrasound (n [%])	154 (51.7)	18 (6.5)	< 0.001

Abbreviations: GOs, Gynecologists/Obstetricians; GPs, General Practitioners; y, years; IQR, interquartile range.

Respondents had been in practice for a median of 6 years (IQR 2;15).

The vast majority of GOs and GPs (93%) considered third trimester ultrasound useful and necessary in the surveillance of low risk pregnancy (Table 8). GPs are very consistent regarding the best time to perform third trimester ultrasound, with 90% defending 30-33 weeks. Among GOs, 38% consider that the best time to perform third trimester screening is 35-37 weeks ($p < 0.001$). Regarding clinical screening of FGR with SFD, GOs and GPs have different opinions (Table 8). GOs (51%) considered that SFD was a measurement with moderate accuracy for screening of FGR while GPs (61%) attributed a low accuracy ($p < 0.001$). Less than 5% of all physicians considered that SFD was a measurement with high accuracy.

Table 8: Opinion of GOs and GPs regarding FGR screening during third trimester in low risk pregnancies

Variables	Gynecologists/ Obstetricians (n = 298)	General Practitioners (n = 275)	*p* value
Accuracy of symphysis-fundus distance in detection of FGR			< 0.001
Null (0%)	20 (6.7)	11 (4.0)	
Low (<10%)	119 (39.9)	167 (60.7)	
Moderate (10 – 90%)	151 (50.7)	92 (33.5)	
High (>90%)	8 (2.7)	5 (1.8)	
Considers that routine third trimester ultrasound is needed	276 (92.6)	256 (93.1)	0.83
Best time to perform third trimester ultrasound			< 0.001
30 – 33 weeks	172 (62.3)	230 (89.8)	
35 – 37 weeks	104 (37.7)	26 (10.2)	
Impact of third trimester ultrasound on cesarean deliveries			< 0.001
Decrease	51 (17.1)	92 (33.5)	
Null	149 (50.0)	71 (25.8)	
Increase	98 (32.9)	112 (40.7)	
Impact of third trimester ultrasound on NICU admissions			0.04
Decrease	127 (42.6)	143 (52.0)	
Null	118 (39.6)	80 (29.1)	
Increase	53 (17.8)	52 (18.9)	

Abbreviations: GOs, Gynecologists/Obstetricians; GPs, General Practitioners; FGR, fetal growth restriction; NICU, neonatal intensive care unit.

GOs and GPs also had different opinions about the impact of routine third trimester ultrasound on cesarean delivery rate for fetal distress. Fifty percent (50%) of GOs considered it would have no impact on cesarean delivery rate for fetal distress, while 41% of GPs considered that it would contribute to increase this rate ($p < 0.001$). Opinions also diverged regarding the impact on admissions of newborns to NICU ($p = 0.04$). The majority of GPs (52%) considered that it would contribute to diminish admissions to NICU while GOs revealed a dichotomy with 43% of respondents reporting that it would diminish the rate and 40% that it would have no impact.

Responses to questions regarding third trimester FGR screening were stratified based on current clinical activity. Eighty-two percent (471/573) of physicians performed weekly surveillance of low risk pregnancies and 30% (172/573) performed weekly obstetric ultrasound.

SFD was considered a measurement with low to moderate accuracy for the screening of FGR by both groups of physicians that performed weekly surveillance of low risk pregnancies (n = 471) and the ones that did not have this activity (n =102). Most physicians in both groups acknowledged the usefulness of routine third trimester ultrasound. There was no statistically significant difference between groups regarding the best time to perform the ultrasound, the impact of routine third trimester ultrasound on the rate of cesarean deliveries and admissions to NICU (Table 9).

Table 9: Opinion of physicians regarding FGR screening during third trimester in low risk pregnancies according to clinical activity

Variables	Surveillance of low risk pregnancies		*p* value	Perform obstetric ultrasound		*p* value
	Yes (471)	No (102)		Yes (172)	No (401)	
Accuracy of symphysis-fundus distance in detection of FGR			0.94			0.67
Null (0%)	24 (5.1)	7 (6.9)		14 (8.1)	17 (4.2)	
Low (<10%)	238 (50.5)	48 (47.1)		75 (43.6)	211 (52.6)	
Moderate (10-90%)	198 (42.0)	45 (44.1)		80 (46.5)	163 (40.7)	
High (>90%)	11 (2.4)	2 (1.9)		3 (1.8)	10 (2.5)	
Considers that routine third trimester ultrasound is needed	440 (93.4)	92 (90.2)	0.25	158 (91.9)	374 (93.3)	0.55
Best time to perform third trimester ultrasound			0.09			< 0.001
30 – 33 weeks	337 (76.6)	63 (68.5)		97 (61.4)	303 (81.0)	
35 – 37 weeks	103 (23.4)	29 (31.5)		61 (38.6)	71 (19.0)	
Impact of third trimester ultrasound on cesarean deliveries			0.37			0.03
Decrease	129 (27.4)	14 (13.7)		39 (22.7)	104 (25.9)	
Null	171 (36.3)	48 (47.1)		78 (45.3)	141 (35.2)	
Increase	171 (36.3)	40 (39.2)		55 (32.0)	156 (38.9)	
Impact of third trimester ultrasound on NICU admissions			0.26			0.13
Decrease	235 (49.9)	35 (34.3)		82 (47.7)	188 (46.9)	
Null	153 (32.5)	45 (44.1)		65 (37.8)	133 (33.2)	
Increase	83 (17.6)	22 (21.6)		25 (14.5)	80 (19.9)	

Abbreviations: GOs, Gynecologists/Obstetricians; GPs, General Practitioners; FGR, fetal growth restriction; NICU, neonatal intensive care unit.

Comparing the group of physicians that performed weekly obstetric ultrasound (n = 172) with the one that did not perform scans (n = 401), both considered that SFD was a measurement with low to moderate accuracy for FGR screening. A higher proportion of physicians that performed obstetric ultrasound considered that the best time to perform the ultrasound was 35-37 weeks, compared with physicians that did not perform obstetric ultrasound (39% *vs* 19%, p < 0.001). Forty-five percent of physicians that performed obstetric ultrasound considered that third trimester scan would have no impact on cesarean delivery rate for fetal distress while 39% of the ones that did not perform scans considered that it would contribute to increase this rate (p = 0.03). Both groups had similar proportion of answers regarding the potential impact of third trimester ultrasound to decrease the rate of admissions to NICU (Table 9).

3.2 Discussion

Nearly 93% of respondents considered that routine third trimester ultrasound is necessary. This high percentage was probably due to the fact that national guidelines recommend third trimester ultrasound in low risk pregnancies. Although metanalysis has failed to demonstrate any real benefit from routine third trimester ultrasound,[9] WHO has recently recommended that it might be useful when performed as an antenatal screening to detect fetal compromise and predict complications in apparently healthy pregnancies.[10]

Few respondents (less than 5%) considered that SFD is a measurement with high accuracy. The different opinion of GOs and GPs was consistent with the literature, that attributes a variable sensitivity to this type of screening, probably because the measurement is not always properly performed and because there are limitations associated with maternal characteristics.[6,7] A prospective outcome study indicated that universal third trimester ultrasound almost tripled the detection of SGA babies compared with clinically indicated sonography with serial measurement of SFD (57% *vs* 20%).[46]

Results from this survey reinforce that, where there are unclear or conflicting recommendations, there are varied and conflicting practices among clinicians. Regarding the best time to perform third trimester ultrasound, a higher proportion of GOs (38%) selected 35-37 weeks as the best time to perform the ultrasound compared to GPs (10%). This difference may be because GOs discuss more frequently this topic at scientific meetings and may be more familiar with recent studies that suggest that an ultrasound after 35 weeks has a higher detection rate of FGR compared with an earlier ultrasound during the third trimester.[72,107]

GOs mainly considered that third trimester ultrasound would have no impact on cesarean delivery rate for fetal distress, probably because they thought that detection of FGR would include two groups of fetuses: a group of FGR that would be timely delivered, thus potentially avoiding later emergent cesarean sections and another proportion of constitutionally small fetuses that could be submitted to iatrogenic obstetric intervention. Similarly, 40% of GOs considered that third trimester ultrasound would have no impact on admissions to NICU, while 43% considered that it could reduce this rate, which may suggest that the ultrasound could help selecting more appropriate surveillance and timely delivery for detected FGR, contributing to lower morbidity.

GPs mainly considered that a routine third trimester ultrasound would contribute to an increase in cesarean rate for fetal distress and would decrease the admissions to NICU. Although we did not ask physicians the reasons behind their choices, we can hypothesize that GPs may have the idea that in case of ultrasound detected FGR, these fetuses may need to be delivered by cesarean section and this would be protective of adverse outcome. Nonetheless, evidence has demonstrated that planned cesarean deliveries are associated with more NICU admissions compared to planned vaginal deliveries.[108]

In our subgroup analysis, physicians that performed obstetric ultrasound more frequently selected 35-37 weeks as the best time to perform the ultrasound compared to physicians that did not perform obstetric ultrasound. Physicians that performed ultrasound may be more updated in terms of recent literature that has attributed a higher detection rate of FGR to a later ultrasound during the third trimester.[72, 109]

The main limitation of our study was the low response rate, particularly the low response rate for GPs compared to GOs, probably because the first are less motivated for this subject since GOs deal more directly with the consequences of missing FGR. Despite the low response rate of GPs, we decided to analyze the data and withheld attempts to include more GPs since we identified important differences among the physicians included.

We may have lost some participants that may have changed e-mail without updating personal information at the registries of scientific societies. A selection bias could be associated with recruitment of physicians that have e-mail as well as physicians that usually attend scientific meetings that may be more motivated to be updated. Implementation of two modalities of recruitment may have minimized the impact of these biases on results.

Although we did not ask practitioners whether they are aware of guidelines for third trimester FGR screening in low risk pregnancies, practice and knowledge variation is apparent and suggests that providers may have controversial ideas about the screening of FGR. These instances indicate the need for further research, both to gain a better understanding of FGR optimal screening and to improve outcomes and optimize guidelines.

4. Part IV: Sonographic evaluation of fetal growth in the third trimester of low risk pregnancy: a randomized trial

4.1 Results

Figure 3 shows a flowchart of the participants and the reasons for exclusion in both groups. A total of 1093 pregnant women were randomized to control (n = 535) and study (n = 558) groups. Of these women, 32 (2.9%) were lost to follow up (2 before the scan and 30 during the scan-to-delivery interval).

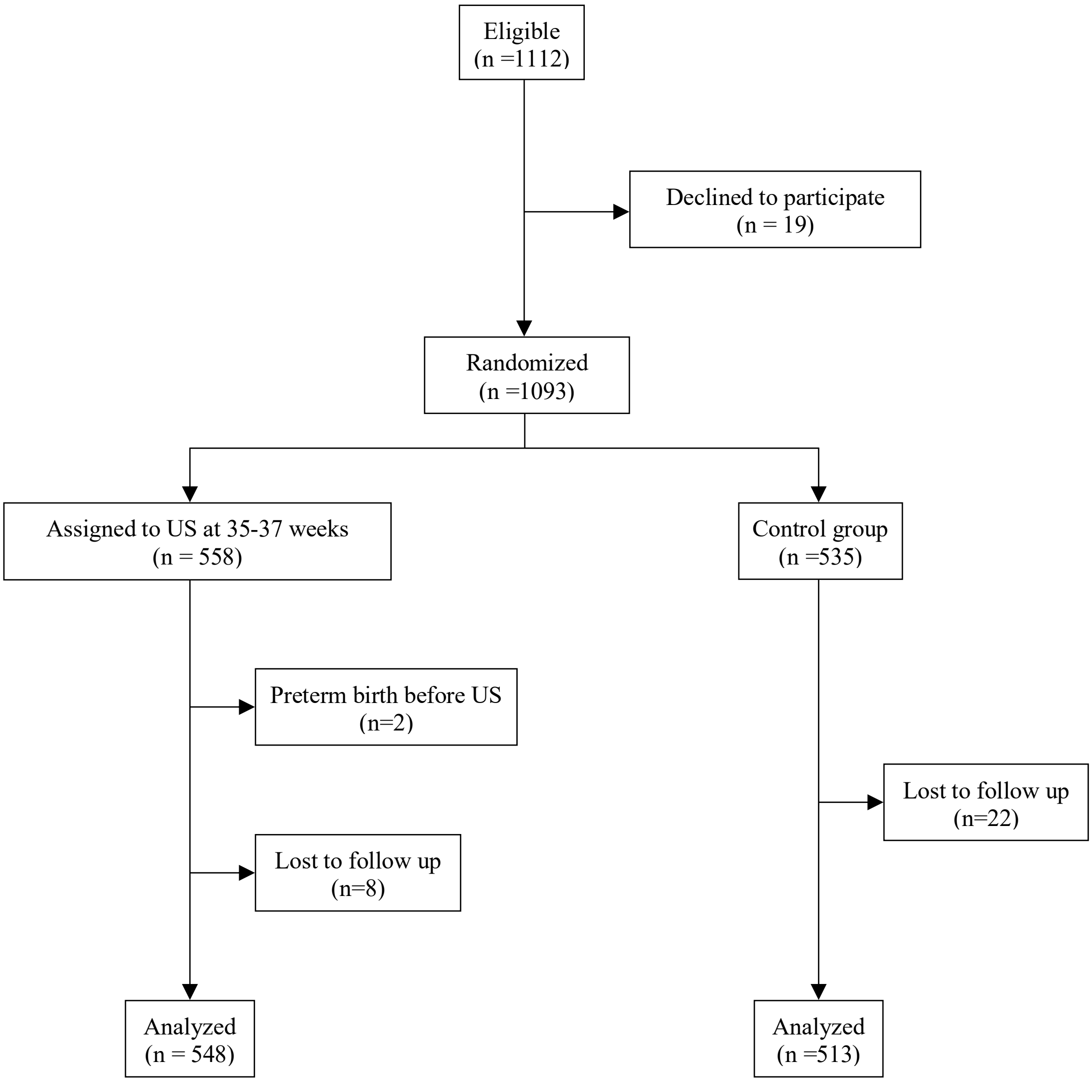

Figure 3: Flowchart summarizing selection and grouping of study and control groups in the randomized trial.

Abbreviations: US, ultrasonography.

Baseline characteristics of participants lost to follow-up were comparable to the 1061 who completed the study, except for a lower maternal age at randomization in the subset lost to follow up (Table 10). Demographic characteristics of the 1061 pregnant women analyzed did not differ between control (n = 513) and study (n = 548) groups (Table 11). Table 12 summarizes perinatal and neonatal outcomes. A total of 98 (9.2%) newborns were found to be SGA (birthweight < 10^{th} centile), with no differences between the two groups. Within the 52 cases of SGA in the study group, the ultrasound at 35-37 weeks` gestation detected 26 (50%). We verified that the rates of operative vaginal and cesarean deliveries were similar for the two groups, while the study group had a lower rate of operative vaginal deliveries for non-reassuring fetal status (24.4% *vs* 39.3%, p = 0.005) and also a lower rate of cesarean deliveries for non-reassuring fetal status (16.8% *vs* 38.8%, p < 0.001), compared to control group (Table 12). No perinatal mortality was registered for both groups.

Table 10: Demographic characteristics of 1093 pregnant women randomly assigned to undergo an additional ultrasound examination at 35-37 weeks´ gestation according to follow up status

Variables	Completed (n = 1061)	Lost (n = 32)	*p* value
Maternal age (y) [median(IQR)]	30 (26-34)	27.5 (25-31.5)	0.02
Maternal height (m) mean ± SD	1.63 ± 0.06	1.64 ± 0.06	0.50
Maternal weight at beginning of pregnancy (Kg) [median(IQR)]	61 (55-70)	60 (56-70)	0.86
Body mass index at beginning of pregnancy (Kg/m^2) [median(IQR)]	23 (20.7-26.2)	22.8 (20.9-25.3)	0.90
Increase in weight during pregnancy at randomization (Kg) [median(IQR)]	11 (9-15)	10 (8-14)	0.65
Parity (n [%])			
Nulliparous	573 (54)	13 (41)	0.61
Multiparous	488 (46)	19 (59)	
Marital status (n [%])			0.08
Single	295 (27.8)	14 (43.7)	
Married	443 (41.8)	6 (18.8)	
Co-habitant	299 (28.2)	12 (37.5)	
Divorced	13 (1.2)	0 (0)	
Widowed	1 (0.1)	0 (0)	
Unknown	10 (0.9)	0 (0)	
Ethnicity (n [%])			0.30
White	939 (88.5)	26 (81.2)	
Black	116 (10.9)	6 (18.8)	
Mixt	2 (0.2)	0 (0)	
Asian	4 (0.4)	0 (0)	
Education (n [%])			0.06
Doctoral level	7 (0.7)	0 (0)	
Master level	44 (4.2)	0 (0)	
Degree level	337 (31.8)	8 (25)	
High school (12th grade)	337 (31.8)	11 (34.4)	
Middle school (9th grade)	256 (24.1)	6 (18.7)	
Elementary school (4th grade)	62 (5.8)	7 (21.9)	
Less than elementary school	10 (0.9)	0 (0)	
Unknown	8 (0.7)	0 (0)	
Smoker at randomization (n [%])	164 (15.5)	6 (18.8)	0.61

Abbreviations: y, years; IQR, interquartile range; SD, standard deviation.

Per protocol, 501 and 510 participants underwent an additional scan at 35-37 weeks´ gestation and were included in the control group (followed the national recommendation of third trimester ultrasound at 30-33 weeks), respectively. Forty-seven (8.6%) participants in the study group did not attend the scheduled ultrasound. In order to minimize this number, we attempted to contact these patients by phone to reschedule the scan, but in 30 patients there was no availability to perform the scan within the gestational age frame defined and 17 patients did not answer the phone. In the control group, three women performed a scan for low SFD and all of these were excluded before per protocol analysis. Baseline characteristics were comparable between groups (Table 13).

Table 11: Demographic characteristics of 1061 pregnant women randomly assigned to undergo an additional ultrasound examination at 35-37 weeks´ gestation (study group) versus 30-33 weeks´ gestation (control group)

Variables	Control group (n = 513)	Study group (n = 548)	*p* value
Maternal age (y) [median (IQR)]	30 (26-35)	30.5 (26-34)	0.93
Maternal height (m) mean ± SD	1.63 ± 0.06	1.63 ± 0.06	0.18
Maternal weight at beginning of pregnancy (Kg) [median (IQR)]	61 (55-70)	60 (54-70)	0.35
Body mass index at beginning of pregnancy (Kg/m^2) [median (IQR)]	23.1 (21-26.3)	22.8 (20.6-26.1)	0.23
Increase in weight during pregnancy at randomization (Kg) [median (IQR)]	11 (9-14)	11 (9-15)	0.67
Parity (n [%])			
Nulliparous	269 (52.4)	304 (55.5)	0.32
Multiparous	244 (47.6)	244 (44.5)	
Marital status (n [%])			0.85
Single	138 (26.9)	157 (28.6)	
Married	212 (41.3)	231 (42.2)	
Co-habitant	149 (29.0)	150 (27.4)	
Divorced	7 (1.4)	6 (1.1)	
Widowed	1 (0.2)	0 (0)	
Unknown	6 (1.2)	4 (0.7)	
Ethnicity (n [%])			0.42
White	457 (89.1)	482 (88.0)	
Black	55 (10.7)	61 (11.1)	
Mixt	0 (0)	2 (0.4)	
Asian	1 (0.2)	3 (0.5)	
Education (n [%])			0.70
Doctoral level	4 (0.8)	3 (0.5)	
Master level	24 (4.7)	20 (3.7)	
Degree level	153 (29.8)	184 (33.6)	
High school (12th grade)	175 (34.1)	162 (29.6)	
Middle school (9th grade)	126 (24.5)	130 (23.7)	
Elementary school (4th grade)	21 (4.1)	41 (7.5)	
Less than elementary school	5 (1.0)	5 (0.9)	
Unknown	5 (1.0)	3 (0.5)	
Smoker at randomization (n [%])	79 (15.4)	85 (15.5)	0.96

Abbreviations: y, years; IQR, interquartile range; SD, standard deviation.

The rate of SGA (birthweight < 10th centile) was similar between study and control groups [50/501 (10%) *vs* 45/510 (8.8%), p = 0.53]. Similarly to the intention-to-treat analysis, the study group had a lower rate of operative vaginal deliveries for non-reassuring fetal status [36/158 (22.8%) *vs* 52/134 (38.8%), p = 0.003] and also a lower rate of cesarean deliveries for non-reassuring fetal status [16/101 (15.8% *vs* 40/103 (38.8%), p < 0.001), compared to the control group (Table 13). For the study group, 31 cases had a diagnosis of FGR (EFW < 10th centile) at the 35-37 weeks' ultrasound. Comparing this group with the group with EFW ≥ 10th centile, the median gestational age at delivery was lower for the FGR group [39 (38-39.6) *vs* 40.1 (39.1-40.6), p <0.001].

Table 12: Perinatal outcomes of 1061 pregnant women randomly assigned to undergo an additional ultrasound examination at 35-37 weeks´ gestation (study group) versus 30-33 weeks´ gestation (control group)

Variables	Control group (n = 513)	Study group (n = 548)	*p* value
Labor induction (n [%])	133 (25.9)	162 (29.6)	0.19
Gestational age at delivery (wk) (median ± IQR)	40 (39-40.5)	40 (39.1-40.5)	0.83
Male gender (n [%])	266 (51.9)	284 (51.8)	0.99
Birthweight (g) (median ± IQR)	3295 (3030-3615)	3282.5 (3035-3620)	0.99
Birthweight centile (median ± IQR)	39.6 (22.7-64.1)	39.2 (21.7-64.9)	0.64
Birthweight			
< 10^{th} centile (n [%])	46 (9.0)	52 (9.5)	0.77
< 3^{rd} centile (n [%])	9 (1.8)	8 (1.5)	0.81
Operative vaginal delivery (n [%])	135 (26.3)	168 (30.7)	0.12
Operative vaginal delivery for non-reassuring fetal status (n [%])	53 (39.3)	41 (24.4)	0.005
Cesarean delivery (n [%])	103 (20)	107 (19.5)	0.82
Cesarean delivery for non-reassuring fetal status (n [%])	40 (38.8)	18 (16.8)	<0.001

Abbreviations: wk, weeks; IQR, interquartile range; SD, standard deviation.

Table 13: Comparison of baseline characteristics and perinatal outcomes of 1011 pregnant women randomly assigned to undergo an additional ultrasound examination at 35-37 weeks´ gestation (study group) versus 30-33 weeks´ gestation (control group) – per protocol analysis

Baseline characteristics	*p* value	Perinatal outcomes	*p* value
Maternal age	0.72	Labor induction	0.10
Maternal height	0.08	Gestational age at delivery	0.22
Maternal weight at beginning of pregnancy	0.46	Male gender	0.73
Body mass index at beginning of pregnancy	0.29	Birthweight	0.82
Increase in weight during pregnancy at randomization	0.64	Birthweight centile	0.67
Parity	0.17	Birthweight < 10th centile	0.53
		< 3rd centile	0.84
Marital status	0.69	Operative vaginal delivery	0.07
Ethnicity	0.60	Operative vaginal delivery for non-reassuring fetal status	0.003
Education	0.98	Cesarean delivery	0.99
Smoker at randomization	0.84	Cesarean delivery for non-reassuring fetal status	<0.001

Considering only the pregnant patients who performed ultrasound at 35-37 weeks' gestation (n = 501), this ultrasound correctly detected 26 cases of FGR that had been missed by the standard 30-33 weeks' gestation ultrasound and also correctly considered 446 cases (EFW ≥ 10^{th} centile) appropriate weight for gestational age which corresponded to newborns with appropriate weight for gestational age at delivery (birthweight ≥ 10th centile), with overall accuracy, i.e. (true positives + true negatives)/all observations of 94% (26+446)/501.

Spearman´s correlation coefficient was higher between the EFW centile at 35-37 weeks' ultrasound and birthweight centile (ρ = 0.75) than the correlation coefficient between the EFW centile at 30-33 weeks' ultrasound and birthweight centile (ρ = 0.44).

For prediction of FGR, area under the receiver-operating characteristics (ROC) curve (AUC) of estimated fetal weight centile at 35-37 weeks' ultrasound was 0.90 (95% CI, 0.86-0.95) (Figure 4). Table 14 demonstrates the performance of the ultrasound for FGR detection.

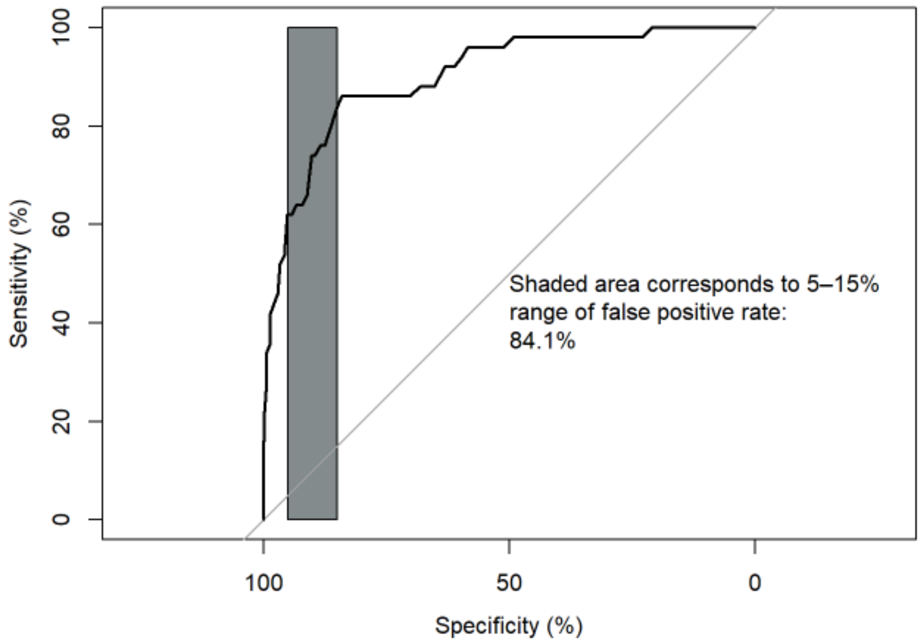

Figure 4: Area under the receiver-operating characteristics curve for ultrasound performed at 35-37 weeks´ gestation for prediction of fetal growth restriction

Table 14: Performance of ultrasound examination at 35-37 weeks´ gestation for detection of fetal growth restriction

	35-37 weeks' ultrasound
Sensitivity (%)	82.3
Specificity (%)	92.6
False positive rate (%)	7.4
Positive predictive value (%)	28.0
Negative predictive value (%)	99.3

4.2 Discussion

This prospective randomized trial provided evidence that performing a routine third trimester ultrasound at 35-37 weeks' gestation had an overall accuracy of 94% for detection of FGR. If we compare this data with our previous retrospective study (Part I), that included low risk pregnancies that only performed the routine third trimester screening at 30-33 weeks' gestation (national guidelines),[71] this earlier ultrasound had a lower overall accuracy of 89%. Moreover, we verified that the study group had better perinatal outcomes, namely lower rate of operative vaginal and cesarean deliveries for non-reassuring fetal status. Given similar baseline characteristics of both groups, gestational age at delivery and also similar rate of SGA newborns between groups, we may hypothesize that the differences in perinatal outcomes are due to our intervention (additional later ultrasound during third trimester). Our results are also in accordance with our previous retrospective study (Part I) that concluded that detected versus nondetected FGR are associated with better perinatal outcomes.

In our series, the AUC of 90% reinforces that an ultrasound at 35-37 weeks' gestation has a good performance for screening of FGR. Previous studies have already demonstrated that FGR detection rate was superior at 36 *vs* 32 weeks' gestation[72]. Nonetheless studies have not demonstrated better perinatal outcomes with this late third trimester ultrasound.[9,72] For one instance, metanalysis have limited contemporary validity as they have used outdated surrogates of fetal growth or protocols in which FGR diagnosis elicited no change in management.[9] Furthermore, some studies have included pregnant women with maternal risk factors diagnosed after randomization which may have introduced a bias in the evaluation of perinatal outcomes.[72] Despite our smaller sample, we have only included low risk pregnancies with no maternal risk factors and we followed a strict protocol after the diagnosis of FGR at 35-37 weeks' gestation ultrasound with well-defined timing and measurements for follow up scans as well as specific gestational ages to schedule delivery. The lower gestational age at delivery for the group with EFW < 10^{th} centile at 35-37 weeks' gestation compared with EFW ≥ 10^{th} centile may reflect the different surveillance and management provided for the first group. Since national guidelines recommend 30-33 weeks' screening ultrasound, we could not have avoided this scan in the study group, so we have only included patients that had already had an appropriate EFW at 30-33 weeks' gestation. This strategy of serial scanning in the study group may have contributed to improve the detection of FGR and also to improve perinatal outcomes.

The higher correlation coefficient between EFW centile at 35-37 weeks' ultrasound and birthweight centile when compared to 30-33 weeks' ultrasound centile is in accordance with data from other studies that concluded that the closer the delivery occurs to the assessment, the higher the predictive performance of the scan.[109,110] We can also add that a later scan during third trimester may be more appropriate to identify fetuses that only begin to decelerate their growth after the scan at 30-33 weeks' gestation. One can argue that if we consider replacing the 30th-33rd weeks' ultrasound by a later scan (35-37 weeks), the delay in the diagnosis of FGR might contribute to adverse perinatal outcomes. We have to acknowledge that our study was underpowered to detect events with low prevalence such as perinatal mortality, but others have already demonstrated that fetal death is higher for FGR in the late term and post term periods than in the preterm period.[111] This data is quite reassuring in terms of risks of adverse outcomes associated with the possibility of delaying the routine third trimester ultrasound and the diagnosis of FGR.

A limitation of our study was the slow recruitment process which led us to stop the trial when we had more than 90% of the planned sample. We consider that this decision does not affect the conclusions of our trial since we found significant differences in the accuracy between 30-33 weeks' and 35-37 weeks' gestation ultrasounds and also important clinical and statistical differences in meaningful perinatal outcomes. Furthermore, the fact that we have only recruited patients in one hospital has contributed to slow recruitment and may hamper generalization of results but has also allowed us to have a very low rate of loss to follow up (2.9%).

Another limitation were the 47 cases that missed the ultrasound scheduled for 35-37 weeks in the study group. However, this may not have had a serious impact on outcome analysis since intention-to-treat and per-protocol analyses provided very similar results.

5. Part V: Different patterns of brain reorganization in small fetuses assessed by neurosonography

5.1 Results

An initial sample of 400 singleton fetuses was included in this cohort, but 82 had to be excluded due to lack of image quality for delineation according to the standards defined. The final cohort comprised a total of 318 fetuses: 97 normally grown and 221 late onset small fetuses, further subdivided into late onset SGA (n = 67) or late onset FGR (n = 154). Baseline maternal characteristics and perinatal outcomes are shown in Table 15.

Maternal characteristics did not differ among groups except for nulliparity that had higher prevalence in SGA and FGR cases. Moreover, similar rates of gestational diabetes and use of IVF techniques was found among groups. As expected, small fetuses showed statistically significant lower birthweight centiles and earlier gestational age at delivery due to clinical management protocol recommending induction of labor earlier in small fetuses. Besides, FGR fetuses exhibited worse perinatal outcomes with higher rates of emergency cesarean sections and pathological Apgar score compared to the other groups.

Table 15: Demographic characteristics and perinatal outcomes

	Control (n = 97)	SGA (n = 67)	FGR (n = 154)	*p* value
Maternal baseline characteristics				
Maternal age (y) [median (IQR)]	34 (30–37)	32 (27-35)	33 (29-36)	0.08
Caucasian ethnicity (%)	65.3	68.2	70.5	0.70
Smoking (%)	16.8	18.2	21.8	0.61
Body mass index (Kg/m^2) [median (IQR)]	22.4 (20.7-25.3)	21.8 (20.0-24.1)	21.7 (19.9-24.0)	0.13
Nulliparity (%)	40.0	60.6*	65.3*	< 0.001
Perinatal characteristics				
In vitro fertilization (%)	4.2	6.3	11.0	0.16
Gestational Diabetes (%)	12.3	8.3	10.8	0.75
Preeclampsia (%)	0	3.0	34.5*$^{¥}$	< 0.001
GA at delivery (wk) [median (IQR)]	39 (38-40)	38 (37-40)*	37 (34-38)*$^{¥}$	< 0.001
Male gender (%)	48.5	49.3	55.6	0.48
Birthweight (g)	3102 (2900-3333)	2680 (2470-2790)*	2050 (1525-2370)*$^{¥}$	< 0.001
Birthweight centile [median (IQR)]	23 (43-17)	5 (4-7)*	1 (0-2)*$^{¥}$	< 0.001
Cesarean section (%)	25.8	20.9	53.9*$^{¥}$	< 0.001
Emergency cesarean delivery (%)	6.7	4.7	17.2*$^{¥}$	0.009
Umbilical artery pH	7.22 (7.19-7.27)	7.24 (7.20-7.28)	7.23 (7.17-7.26)	0.16
5 min Apgar score < 7 (%)	0	0	2.0*$^{¥}$	0.31

Abbreviations: SGA, small for gestational age; FGR, fetal growth restriction; y, years; IQR, interquartile range; GA, gestational age; wk, weeks; g, grams.

* p < 0.05 as compared to controls.

$^{¥}$ p < 0.05 as compared to SGA.

Regarding NSG parameters we observed that FGR presented larger insula depth/BPD [0.34 (0.33-0.34) *vs* 0.33(0.31-0.34); p = 0.001], reduced Sylvian fissure depth/BPD [0.14±0.02 *vs* 0.15±0.02; p = 0.003] and shorter CC length/CIX [0.47 (0.45-0.51) *vs* 0.50 (0.48-0.53); p = 0.03] compared to controls. However, measurement of parieto-occipital fissure and vermis did not differ between both groups. We observed two different patterns of changes in SGA and FGR (Table 16 and Figure 5). Whereas similar changes in insula depth were observed in both groups of small fetuses compared to controls, Sylvian fissure and CC length were only significantly different in FGR group. Interestingly, we found a significant linear trend across the severity in the three parameters.

Table 16: Neurosonographic parameters among the study groups

	Control (n = 97)	SGA (n = 67)	FGR (n = 154)	Linear tendency *p* value§
GA at scan (wk) [median (IQR)]	33 (31-36)	34 (31-36)	33 (31-36)	0.94
BPD (mm) [median (IQR)]	80 (72-84)	79 (71-85)	78 (72-83)	0.16
Insula depth/BPD [median (IQR)]	0.33 (0.31-0.34)	0.34 (0.32-0.35)*	0.34 (0.33-0.35)*	0.006
Sylvian fissure depth/BPD (mean ± SD)	0.15 ± 0.02	0.14 ± 0.03	0.14 ± 0.02*	0.003
Parieto-occipital fissure depth/BPD [median (IQR)]	0.05 (0.04-0.06)	0.05 (0.04-0.06)	0.05 (0.04-0.07)	0.76
Corpus callosum length/CIX [median (IQR)]	0.50 (0.48-0.53)	0.50 (0.49-0.53)	0.47 (0.45-0.51)*¥	0.005
Vermis heigh/BPD [median (IQR)]	0.25 (0.24-0.27)	0.25 (0.24-0.27)	0.25 (0.23-0.26)	0.56

Abbreviations: SGA, small for gestational age; FGR, fetal growth restriction; GA, gestational age; wk, weeks; IQR, interquartile range; BPD, biparietal diameter; SD, standard deviation; CIX, cephalic index.

§ Linear tendency *p*-value was calculated by linear regression across the study groups.

* $p < 0.05$ as compared to controls.

¥ $p < 0.05$ as compared to SGA.

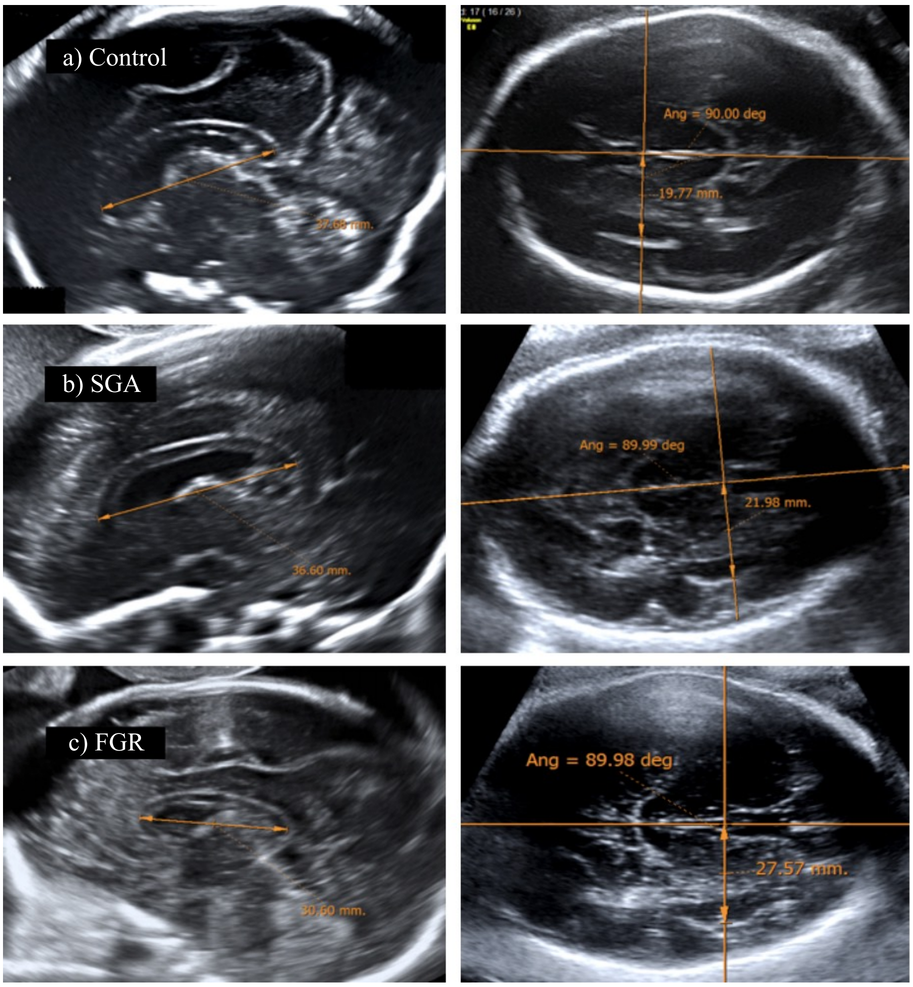

Figure 5: Illustrative neurosonography images performed in the study groups. Left column: Mid-sagittal view of the corpus callosum showing length measurement. Right column: Axial transthalamic plane showing assessment of insular lobe depth measurement. (a) control subject, (b) SGA subject, and (c) FGR subject.

Abbreviations: SGA small for gestational age; FGR, fetal growth restriction.

5.2 Discussion

This prospective study provides evidence that late onset small fetuses present differences in cortical development and CC development compared to controls, suggesting certain degree of brain reorganization that could be demonstrated by ultrasound. We also observed that CC was only affected in FGR, the most severe cases, suggesting a different pattern of effects in this subgroup of small fetuses.

Our results are in line with previous data reporting specific neurostructural changes in fetuses with FGR. Previous studies have demonstrated that preterm FGR infants presented differences in grey matter (GM) and white matter (WM) volumes[112] together with changes in cortical development[78] and brain connectivity.[75] Overall, FGR infants have been associated with decreased total brain and cortical GM volumes with significantly smaller brain volume.[113,114] These structural changes have also been seen in the prenatal period with a different pattern of cortical development, specially the insular cortex, compared to normally grown babies.[115] Our study goes beyond trying to better characterize neurostructural changes of both groups of small fetuses, SGA and FGR. We observed two different patterns that shared altered cortical development, the length of the CC, only smaller in FGR fetuses being the differential point between both groups. Brain development is a complex process involving the maturation and functional specialization of GM regions (cerebral cortex and central gray nuclei) and the establishment and myelination of WM connections between the different brain regions.[116-118] Indeed, cortical folding is a dynamic process that starts around 18 weeks of pregnancy and continues until the postnatal period, with its critical period for the emergence of secondary cortical folds from 26 to 36 weeks.[119] Similarly, WM maturation starts during the third trimester and persists during the first years of life, being also particularly vulnerable to hypoxia.[118] CC is the major commissure connecting both cerebral hemispheres and callosal connections begin more centrally in the hippocampal primordium progressing bidirectionally both anterior and posterior, with a more prominent anterior growth.[120] The impact of adverse intrauterine environment on CC development has been demonstrated by the intrinsic vulnerability to chronic hypoxia of immature oligodendrocytes and callosal fibers,[121,122] and by the myelination deficits in the CC of rats exposed to hypoxia, resulting in smaller CC.[123] Whereas both groups of small fetuses presented different cortical maturation, only FGR exhibited shorter CC. This finding supports the hypothesis that those cases exposed to higher level of hypoxia, suffer more impact on WM regions. According to our results, SGA fetuses also exhibited certain degree of brain reorganization with differences in Insular fissure development but without repercussion in WM as they presented normal CC structure. These findings challenge the concept of ´constitutionally small` in concordance with other previous studies that showed changes of fetal brain metabolism, microstructure and suboptimal postnatal neurodevelopment in SGA cases.[74,124,125] Even if this study does not contribute to clarify the nature of SGA *vs* FGR, this evidence supports the hypothesis that SGA fetuses suffer some degree of placental insufficiency, which is not sufficient to show Doppler alterations or severe adverse perinatal outcomes, but enough to produce certain structural and functional brain changes less severe than those observed in FGR. Further physiological studies are required to find out the possible different etiologies and mechanisms involved in fetal smallness.

Despite NSG being a cheap and easily available imaging technique in clinical practice, there is only one study assessing cortical development in small fetuses using this technique.[126] This study mainly described an accelerated cortical maturation in FGR cases compared to controls assessed by cortical grading. Moreover, that study included only 20 cases of early onset FGR compared to our bigger prospective cohort including 221 late onset small fetuses subdivided into SGA and FGR.[126]

From a clinical point of view, given the high prevalence of late onset small fetuses and its consequences on neurodevelopment[127,128] and the fact that NSG is a useful tool that allows us to detect subtle differences in brain structure, evaluation of cortical development and CC could help us to detect those small fetuses with brain reorganization in order to perform early neurodevelopmental screening.

This study has several strengths and limitations. Among the strengths, this is the first study examining cortical development by NSG in late onset small fetuses and therefore showing different patterns of brain reorganization in SGA and FGR by NSG. Moreover, we present a big prospective well-defined cohort characterized prenatally in which a detailed NSG was performed. With regards to limitations, we acknowledge that postnatal neurodevelopmental outcomes were not evaluated, which prevented us from assessing correlation with postnatal performance. Nevertheless, previous MR studies have demonstrated that cortical morphometry was significantly different in late onset SGA fetuses and correlated with poorer neurobehavioral performance.[115] Further studies are necessary to confirm such association when cortical development is evaluated by NSG.

We conclude that late onset small fetuses presented significant differences in the cortical development whereas only FGR showed changes in CC development. Our findings support that NSG could be considered aa a valid tool to detect subtle brain differences in fetuses exposed to late onset growth restriction.

CHAPTER 5

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

There is uncertainty in the literature as to the best approach for identifying SGA fetuses and FGR, especially late onset FGR which represents the majority of FGR. Reasons for this difficulty include controversy on universal *vs* selective ultrasound examination and limited data on the best time for a universal third trimester scan at 32 *vs* 36 weeks' gestation. Based on the Portuguese national guidelines, our retrospective data (Part I) showed a 21% detection rate of SGA with a third trimester screening ultrasound at 30-33 weeks' gestation. We also verified that antenatal detection of SGA is associated with better perinatal outcomes compared with undetected SGA. The recommendation of our national guidelines for a universal ultrasound during third trimester has been reinforced by studies that reported improved prediction of SGA compared with selective ultrasound based on maternal risk factors and measurements of SFD.[46] As for the issue of the best gestational age for the third trimester scan, there is some evidence that the predictive performance of a scan at 36 weeks may be superior to that at 32 weeks.[72,110]

With the aim of improving our national guidelines, we tested the hypothesis of a better predictive performance of a later third trimester screening of FGR with Part II and Part IV studies of this thesis which evaluated precision and accuracy of this later ultrasound, respectively. With Part II study we demonstrated a high intra and inter-observer reproducibility of third trimester ultrasound fetal biometric measurements, even for overweight women, which enabled us to assume that ultrasound at 35-37 weeks' gestation may be performed by different sonographers with high reproducibility. The importance of evaluating reproducibility is based on the need of quality control in fetal biometry for auditing and monitoring purposes and if we want to improve national screening of late FGR in low risk pregnancies we should provide data reassuring that the new methodology can be correctly performed by different operators.

In parallel with the randomized trial, we assessed the opinion of GOs and GPs about third trimester FGR screening with distribution of surveys in order to collect a cross-sectional opinion of physicians on the most accurate method of third trimester FGR screening for low risk pregnancies. Controversial results reflect the lack of consensus on the topic, but we have verified that globally a higher percentage of GOs considered that 35-37 weeks' ultrasound is more accurate to detect FGR than 30-33 weeks when compared to GPs' opinion. Among GOs, clinicians that performed obstetric ultrasound more frequently selected 35-37 weeks as the best time to perform the ultrasound compared to physicians that did not perform obstetric ultrasound. We consider this type of epidemiological studies important to understand the confidence that physicians have in national guidelines and their opinion about the impact that some recommendations have in clinical practice.

Our randomized trial (Part IV study) demonstrated high accuracy of the EFW centile at 35-37 weeks' gestation in predicting the birthweight centile and detecting FGR, with an overall accuracy of 94% and an AUC of 90%. In accordance with recent literature,[72,110] we verified that a later ultrasound during third trimester is better regarding the correlation of EFW with birthweight centiles. Furthermore, the group submitted to an additional ultrasound at 35-37 weeks' gestation had lower rates of operative vaginal and cesarean deliveries for non-reassuring fetal status, reinforcing the conclusions of our retrospective data that antenatal identification of FGR allows close monitoring and appropriate management, which may prevent the need for emergent obstetric intervention during labor and delivery. In our national survey (Part III), GOs mainly considered that third trimester ultrasound would have no impact on cesarean delivery rate for fetal distress, probably because they thought that detection of FGR would include two groups of fetuses: a group of FGR that would be timely delivered and avoiding later emergent cesarean sections and another proportion of constitutionally small fetuses that could be submitted to unnecessary iatrogenic obstetric intervention. However, the conclusions of the randomized trial highlight that even for constitutionally SGA, antenatal detection may contribute to improved perinatal outcomes. We must acknowledge that an additional ultrasound during the third trimester involves constrains in terms of human and economic resources. However, we also should consider the potential reduction of costs from reducing obstetric intervention during delivery, a topic to be explored in future research.

Regarding the methodology used at the 35-37 weeks' ultrasound, we chose to use EFW because it allows clinicians to summarize fetal growth and use the same anatomic parameter for monitoring growth prenatally and postnatally (i.e. weight) and also because it is an intelligible measurement when we need to communicate with parents about the perspectives and anticipated birthweight. However, we acknowledge that the use of EFW has also disadvantages such as: errors in single-parameter measurements may be multiplied and the errors are also relatively larger in the fetuses of greatest interest, i.e. those that are SGA or LGA, being higher than the rate of 10–15% that is commonly accepted.[70,129,130] Also, very different fetal phenotypes can have the same EFW (i.e. a fetus with large HC and small AC may have the same EFW as a fetus with small HC and large AC).

In order to calculate EFW, we used the formula of Hadlock *et al.* published in 1985.[24] According with the study of 5163 singleton pregnancies with fetal biometries obtained between 22 – 43 weeks' gestation and live birth, this is the most accurate formula for prediction of birthweight and even for the assessment of a fetus suspected to be either small or large.[131] Centiles or Z-scores are measures of deviation from the mean of a population, under the assumption of underlying normality of distribution of the measured parameter. For the comparison of the EFW with birthweight we have used centiles because they are intuitively more understandable than Z-scores.

For the definition of FGR, we chose ACOG definition[11], since at the beginning of the studies included in this thesis this was the definition which had the most consensus in literature and was most widely used, allowing comparison between series and studies. We acknowledge that this definition includes two different types of fetuses: one group that is not achieving its genetic potential of growth (true FGR) and another group including fetuses that are only constitutionally small for gestational age. According to recent ISUOG guidelines,[70] the lower the cut-off of EFW, the higher the risk of true FGR and as stated in the international Delphi consensus,[57] the EFW below the 3rd centile may be used as the sole diagnostic criterion for FGR and in case of EFW below the 10th centile, the diagnosis of FGR should be considered only in association with other parameters. All these guidelines were published after the beginning of this thesis and the use of a lower cut off would underpower our statistical comparisons. We anticipate that if we considered FGR as EFW < 3rd centile (more serious cases), the differences in perinatal outcomes by using an additional and later third trimester ultrasound would remain with a larger sample size.

Besides the controversy on the best definition of FGR, there is also no consensus about the optimal approach and follow up for these fetuses. In accordance with recent ISUOG guidelines[70], there should be timely referral to an appropriate unit for individualized management that may include antenatal testing strategies such as amniotic fluid assessment, evaluation of Doppler indices of the UA, MCA or a combination of the two (CPR). An advantage of our trial is that we had a well-defined protocol of surveillance for antenatally detected FGR.

In our randomized trial, the study group was submitted to serial sonographic assessment of fetal size over the third trimester allowing the detection of additional cases of FGR that had not been previously detected by the standard third trimester ultrasound at 30-33 weeks' gestation and the improvement on perinatal outcomes. However, we have to acknowledge the possibility of introducing errors and approximations at each step of such a process. The concept of fetal growth velocity, typically represented as deviation from growth-velocity charts (change in centiles or Z-score with advancing gestation), is particularly relevant for assessing fetal growth, rather than fetal size. Some authors,[132,133] but not all,[47,134] have reported that reduced third trimester growth velocity is associated with an increased incidence of certain adverse pregnancy outcomes. According to ISUOG guidelines,[70] fetal growth analysis may help in the management of pregnancy and this concept has been also highlighted in the recommendations of the Delphi consensus[57], namely that a drop of more than two quartiles (or more than 50 centiles) can be used as a criterion for FGR. Overall, clinical implementation of growth velocity will depend on local practice and institutional guidelines and since it has not added significant information to growth assessment, the relationship between growth velocity and the detection of FGR at risk for adverse outcomes requires additional investigation.

In our prospective randomized trial, we used the Yudkin population growth curves,[88] since these are the curves used in our Department for the routine third trimester screening ultrasound and also the ones widely used in our country, as they are the reference included in a highly disseminated software (Astraia®) used for ultrasound archiving and report. Compared with population reference charts, a customized chart will assign a different proportion of fetuses as SGA at birth. This may be relevant to units in which the antenatal population is diverse with respect to those factors, by better capturing fetuses at risk of perinatal complications, but the benefit of such a customized approach over population-based charts in terms of identifying the FGR at risk of adverse perinatal outcomes was not demonstrated in recent studies.[135,136]

Only after the beginning of the studies included in this thesis did Sousa-Santos *et al* develop and validate a fetal growth/birthweight reference curve for the Portuguese population.[137] We acknowledge that the centiles published by these authors are useful by providing real and unbiased data to be interpreted in our population. However, we consider that the use of non-adapted Yudkin`s curves has not introduced such a significant error of interpretation of the results and conclusions of our studies since Sousa-Santos` curves only show subtle differences compared with Yudkin´s.[137] In terms of future research, it would be interesting to investigate if our results do remain after conversion of EFW into centiles with the Portuguese curves` formula.

The choice of growth curves is a challenging topic in FGR research because there is no consensus on the best curve to use and the type of curve selected will influence the percentage of FGR identified. Different studies used different curves which also biases comparisons. Recently, the Fetal Medicine Foundation published fetal and neonatal population weight charts, including 95,579 pregnant women from two maternities in the UK.[138] The innovative aspect of these charts is that before 37 weeks, the authors included the weight of fetuses that still remained *in utero*. The rationale behind this decision is that most fetuses born before 37 weeks correspond to pathological fetuses with abnormal growth. By including the weight of fetuses that remain in utero before 37 weeks, we can minimize the under diagnosis of FGR before 37 weeks that is common with curves that use preterm birthweight.[138] In conclusion, for preterm pregnancies, Fetal Medicine Foundation curves appear to be the most appropriate to use. After 37 weeks neither population nor customized are superior in identifying FGR at increased risk of adverse perinatal outcomes. From a research perspective, choosing international population growth curves seems a reasonable option because it allows meaningful comparisons of FGR rates between countries and before/after birth.

Current research on FGR has focused on the poorer outcome of fetuses with EFW below the 10th centile and abnormal Doppler measurements. However, there are still babies born with birthweight above the 10th centile whose postnatal outcome is inexplicably poor. Though controversial, some series have shown that 60-70% of stillbirths may occur in fetuses whose birthweight falls within the normal range, but who do not reach their growth potential.[139]

Given this heterogeneity of groups defined by EFW/birthweight, it may be necessary to study individual fetuses using additional anatomical parameters or parameter sets. This was the rationale for our Part V study, using NSG to compare normal grown fetuses with FGR and we have concluded that late onset small fetuses had significant differences in cortical development and corpus callosum. This reinforces the importance of complementary methods of studying FGR such as NSG, which could help us to stratify these fetuses and, in the future, to study the potential meaning of these changes regarding neurodevelopment of children. Some studies have already demonstrated that, compared with normal-sized babies, full-term SGA infants, without placental insufficiency have lower 2-year and 10-year neurodevelopmental scores.[126,127] There is a lack of evidence to confirm if prenatal neurosonographic differences between appropriate weight fetuses and FGR correspond to postnatal differences in neurodevelopmental scores.

Besides the concern with optimizing the diagnosis of FGR, improvement in knowledge about the etiology will help us to decrease adverse outcomes. The placenta plays a key role in abnormal growth, especially well-defined for early onset FGR. FGR has been included in placental syndromes based on the theory that inadequate trophoblastic invasion of the spiral arteries, with incomplete arterial remodeling would contribute to increased resistance of the placental circulation and a biochemical response, resulting in endothelial dysfunction, fetal hypoperfusion and FGR.[140] Nonetheless, most cases of late onset FGR are associated with histologically normal placentas and, in the small number of cases showing anomalies, these correspond mainly to massive perivillositary deposition of fibrin, histological findings associated with maternal hypoperfusion.[141,142] Another factor that suggests an alternative etiology for the placental theory is the previous demonstration of the association between FGR and changes in vascular resistance in distinct arterial territories from uterine arteries, such as the ophthalmic artery, which may be justified by primary dysfunction of the maternal hemodynamic adaptation to pregnancy.[143,144] Studies that evaluated maternal cardiac function at 35-37 weeks' gestation have suggested a positive association between maternal cardiac output and heart rate with birthweight. Conversely, a negative association between maternal peripheral vascular resistance and mean arterial pressure with birthweight has been suggested.[145] Physiological cardiovascular changes of pregnancy include plasma volume expansion (peaking at about 32-34 weeks) and generalized peripheral vasodilation (probably triggered by placental angiogenic growth factors), which implies a secondary increase in cardiac output. However, it is difficult to determine the threshold between what we consider to be physiological adaptation and evidence of pathology. We may hypothesize that in late FGR there may occur a lower expansion of plasma volume, with secondary decrease in preload and cardiac output. In parallel, an increase in peripheral vascular resistance may occur due to increased blood viscosity due to decreased volume expansion and/or decreased placental angiogenic factors. Increased peripheral vascular resistance may lead to increased afterload, left ventricular hypertrophy and abnormal cardiac remodeling. Some studies have shown findings of left ventricular hypertrophy and eccentric ventricular remodeling in apparently normal pregnancies and, even in some cases, diastolic dysfunction, in a higher degree than that found in high-competition athletes or in some pathological conditions outside pregnancy.[146]

As a future line of research to the studies included in this thesis, in collaboration with the Department of Cardiology of HSM-CHULN, we have designed a study to evaluate whether maternal hemodynamic cardiovascular changes during the third trimester of low risk pregnancies may be associated with FGR and may contribute to improve the diagnosis. This is a prospective observational study that includes low risk pregnant women who perform screening ultrasound of FGR at 35-37 weeks' gestational age and that undergo an echocardiogram at the same week of the obstetric ultrasound and a control echocardiogram 6 weeks after delivery.

Our main objectives are:
- to evaluate the incidence of late maternal echocardiographic changes in low risk pregnancies;
- to assess whether there is a correlation between EFW and/or Doppler parameters obtained at obstetric scan and maternal cardiovascular function assessed by echocardiogram;
- to assess if potential changes in maternal cardiovascular function during pregnancy remain 6 weeks postpartum.

This study is in the phase of recruiting patients.

Concluding Remarks

In conclusion, ultrasound remains the mainstay of diagnosis in fetal growth anomalies and EFW is the most widely used parameter to detect abnormal growth. In a country that recognizes the value of routine third trimester ultrasound screening of FGR for low risk pregnancies, our data is important to reinforce international studies that have shown that a later ultrasound during the third trimester has a higher accuracy for the detection of FGR; it is a precise exam and it has a high correlation between EFW and birthweight centiles. Furthermore, according to our data it may also contribute to diminish adverse perinatal outcomes compared to an earlier ultrasound during third trimester. This data may lead to changes in national guidelines of surveillance of low risk pregnancies, namely the National Health Authority may consider delaying the recommended gestational age for routine third trimester ultrasound.

The differences in neurosonographic patterns between appropriate weight fetuses and FGR reinforces the concept that fetal biometry should represent only one of the elements of the screening for abnormal growth and that improved FGR screening may be feasible by using a combined approach that includes biometry as well as other clinical, biological and/or imaging markers.

By providing a better comprehension of FGR diagnosis and etiology, we further support the importance of research regarding the relationship between abnormal fetal growth and future children and adult health. Future research should include more accurate prenatal sonographic detection of FGR in order to help us identifying a small fetus at risk for morbidity and mortality and also to determine interventions that could improve neonatal outcomes.

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ANNEXES

List of publications included in the Thesis

Peer - reviewed original research articles

1. Policiano C, Fonseca A, Mendes JM, Clode N, Graça LM. Small-for-gestational-age babies of low-risk term pregnancies: does antenatal detection matter? J Matern Fetal Neonatal Med. 2018;31(11):1426-1430. doi: 10.1080/14767058.2017.1317741.

2. Policiano C, Mendes JM, Fonseca A, Barros J, Martins D, Reis I, Clode N, Graça LM. Impact of maternal weight on the intra-observer and inter-observer reproducibility of fetal ultrasonography measurements in the third trimester. Int J Gynaecol Obstet. 2018;140(1):53-59. doi: 10.1002/ijgo.12333.

3. Policiano C, Reis-de-Carvalho C, Clode N, Mendes Graça L. National-survey for evaluation of the best screening method of late fetal growth restriction in low risk pregnancy: a prospective study. Eur J Obstet Gynecol Reprod Biol. 2019;240:187-191. doi: 10.1016/j.ejogrb.2019.07.009.

Original articles under submission

1. Policiano C, Mendes JM, Fonseca A, Barros J, Reis-de-Carvalho C, Cal M, Vargas S, Martins D, Reis I, Clode N, Graça LM. Sonographic evaluation of fetal growth in the third trimester of low risk pregnancy: a randomized trial.
Submitted to American Journal of Obstetrics and Gynecology in June 2020

2. Paules C, Miranda J, Policiano C, Crovetto F, Youssef L, Hahner N, Crispi F, Gratacos E, Eixarch E. Different patterns of brain reorganization in small fetuses assessed by neurosonography.
Submitted to Ultrasound in Obstetrics & Gynecology in September 2020

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE, 2017
http://dx.doi.org/10.1080/14767058.2017.1317741

ORIGINAL ARTICLE

Small-for-gestational-age babies of low-risk term pregnancies: does antenatal detection matter?

Catarina Policiano[a], Andreia Fonseca[a], Jorge M. Mendes[b], Nuno Clode[a] and Luís M Graça[c]

[a]Department of Obstetrics and Gynecology, CHLN-Hospital Universitário de Santa Maria, Lisbon, Portugal; [b]NOVAIMS, Universidade Nova de Lisboa, Lisbon, Portugal; [c]Faculdade de Medicina da Universidade de Lisboa, CAM-Centro Académico de Medicina de Lisboa, Lisbon, Portugal

ABSTRACT

Objectives: To compare delivery route and admission rate to neonatal intensive care unit between small- and appropriate-for-gestational-age babies among low-risk term pregnancies.
Methods: A retrospective study was conducted using the database of deliveries in 2014 at a tertiary hospital. Babies delivered at ≥37 weeks with birthweight <10th centile were considered small-for-gestational-age (SGA) and >90th centile were considered large-for-gestational-age. Fetal weight estimation at 30–33 weeks ultrasound <10th centile was considered antenatal detection of SGA.
Results: Among 1429 low-risk term pregnancies, 11% (151/1429) had SGA babies and 5% (75/1429) had large-for-gestational-age. SGA babies were associated with higher rate of cesarean sections for nonreassuring fetal status (18/151 versus 8/1202, $p < .001$) and higher rate of admissions to neonatal intensive care unit (16/151 versus 18/1202, $p < .001$) compared to appropriate-for-gestational-age. Within SGA group, antepartum detected fetuses were associated with lower rate of operative deliveries for nonreassuring fetal status than undetected group (3/31 versus 39/120, $p = .01$)
Conclusions: In our series, women with SGA term babies were associated with more adverse obstetric and neonatal outcome than appropriate-for-gestational age, especially among those undetected prenatally.

ARTICLE HISTORY
Received 12 January 2017
Revised 3 April 2017
Accepted 6 April 2017

KEYWORDS
Small-for-gestational-age; antenatal screening; cesarean delivery; nonreassuring fetal status; neonatal intensive care unit admission

Introduction

There is no consensus on the need for a third trimester ultrasound with the aim of screening for fetal growth restriction in low-risk pregnancies and evidence has not provided objective advantages on maternal-fetal outcomes. Nonetheless, a recent large study has demonstrated that for low-risk term pregnancies, small- compared to appropriate-for-gestational-age babies have a significantly higher likelihood of composite neonatal morbidity, stillbirth, and neonatal mortality [1].

Fetal growth restriction (FGR) without prenatal diagnosis is associated with a higher risk of adverse neonatal outcomes (Apgar score at 5 min <4, neonatal seizures, acidosis and neonatal death) compared with fetuses whose diagnosis of FGR was made antepartum [2,3]. Death of a growth-restricted fetus is the second most common etiology of stillbirth. Moreover, a significant proportion of term stillbirths correspond to undiagnosed late FGR [4–6]. Sonographic fetal weight estimation at the last weeks of third trimester in low-risk pregnancies is an effective method for diagnosis of FGR permitting a close surveillance and timely delivery [7,8]. The need for a systematic ultrasound evaluation at the last weeks of a low-risk pregnancy and the best time to perform it remains controversial. The most commonly used clinical screening tool is the serial measurement of symphysis-fundus distance, which is a method of low sensitivity [9,10].

Therefore, the main aim of this study was to compare the delivery route and admission rate to neonatal intensive care unit between small- and appropriate-for-gestational-age babies in low-risk term pregnancies. Secondary outcomes included a subgroup analysis of delivery route and admission to neonatal intensive care unit between antenatally detected and undetected small-for-gestational-age (SGA) babies.

Methods

A retrospective study was conducted at a tertiary hospital using the database of deliveries during the year 2014.

CONTACT Catarina Policiano catarinapoliciano@gmail.com Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal

The study was approved by the local Ethics Committee and is included in an investigation project of third trimester fetal growth restriction screening, funded by FCT (Fundação para a Ciência e Tecnologia).

Low-risk pregnancies with term delivery were selected. Babies with delivery at ≥37 weeks with birthweight <10th centile were considered SGA and with birthweight >90th centile were considered large for gestational age. Birthweight centiles were calculated using reference curves [11]. Medical records were revised in order to collect clinical data including maternal age, parity, gestational age at delivery, induction of labor, birthweight, third trimester ultrasound details, delivery route, and admission of babies to neonatal intensive care unit.

Exclusion criteria were: no register of third trimester ultrasound in medical records, large for gestational age, diabetes, hypertensive disorders of pregnancy, multiple gestation, autoimmune disease, previous pregnancy with fetal growth restriction or preeclampsia, placental abnormalities, fetal malformations, chromosomal anomalies, and TORCH infections.

National guidelines for surveillance of low-risk pregnancies recommend a third trimester ultrasound for fetal growth restriction screening performed at 30–33 weeks. For every fetus, biometric measurements included biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). A combination of these biometric parameters is used in the Hadlock formula that is incorporated in the ultrasound equipment package (GE Voluson E8) and gives us the estimated fetal weight (EFW) in gram (g) and the correspondent centile for gestational age. Fetal weight estimation at 30–33 weeks ultrasound <10th centile was considered antenatal detection of SGA. SGA babies with a 30–33 weeks ultrasound ≥10th centile were considered antenatal nondetected SGA.

The route of delivery (spontaneous vaginal, operative vaginal or cesarean delivery) and indications for cesarean and operative vaginal deliveries were compared between the SGA babies ($n = 151$) and appropriate-for-gestational-age babies ($n = 1202$). Nonreassuring fetal status was defined by the interpretation of continuous cardiotocography, using the ACOG classification [12].

Statistical analysis was performed using Chi-square and Fisher's exact tests to compare categorical data and Student's *t*-test to compare the means within groups. p Values $< .05$ were considered statistically significant. Data processing was carried out using STATA 14.1 (StataCorp, College Station, TX).

Results

During the year 2014, there were 2193 deliveries at our hospital, with 539 cesarean deliveries (25%) and 620 operative vaginal deliveries (28%). In total, 1429 (65%) corresponded to low-risk term pregnancies. Within these, 11% (151/1429) had SGA babies, 5% (75/1429) had large for gestational age and 84% (1202/1429) had adequate weight for gestational age (AGA) babies. Low-risk term pregnancies had a cesarean delivery rate of 18% (256/1429). We excluded the 75 cases of large for gestational age from the analysis.

Clinical characteristics of the women who had SGA babies ($n = 151$) and women with babies with AGA ($n = 1202$) are presented in Table 1. Both groups had a majority of nulliparous women included. Nonetheless, AGA babies group had a statistically significant higher proportion of multiparous than the SGA group (44% versus 30%, $p = .01$). However, the proportion of multiparous with previous cesarean delivery was not statistically different between the two groups. SGA group had a statistically significant lower mean gestational age at birth than AGA (39.1 versus 39.6 weeks). Induction of labor had been more frequently decided in the SGA group than in the AGA. In the former group a large proportion of inductions of labor were

Table 1. Comparison of demographic characteristics and obstetric outcomes between women with small babies and women with adequate weight babies.

Variables	Small-for-gestational-age babies ($n = 151$)	Adequate weight for gestational age babies ($n = 1202$)	p value
Maternal age (y) (mean ± SD)	29.7 ± 6.3	30.2 ± 6.0	.29
Parity (n [%])			
Nulliparous	106 (70)	668 (56)	.01
Multiparous	45 (30)	534 (44)	
Previous cesarean delivery	16 (11)	127 (11)	.99
Gestational age at delivery (wk) (mean ± SD)	39.1 ± 1.4	39.6 ± 1.1	<.001
Induction of labor n (%)	64 (42)	285 (24)	<.001
Operative vaginal rate (n [%])	40 (26)	368 (31)	.30
Operative vaginal for nonreassuring fetal status (n [%])	24 (16)	12 (1)	<.001
Cesarean section rate (n [%])	35 (23)	218 (18)	.13
Cesarean section for nonreassuring fetal status (n [%])	18 (12)	8 (1)	<.001
Admission to neonatal intensive care unit (n [%])	16 (11)	18 (1)	<.001

Table 2. Comparison of demographic characteristics and obstetric outcomes between antepartum detected versus nondetected small-for-gestational-age babies.

	Antepartum detected SGA ($n = 31$)	Antepartum nondetected SGA ($n = 120$)	p
Maternal age (y) (mean ± SD)	29.2 ± 6.4	29.8 ± 6.3	.69
Parity (*n* [%])			
Nulliparous	25 (81)	81 (67)	.15
Multiparous	6 (19)	39 (33)	
Gestational age at delivery (wk) (mean ± SD)	37.8 ± 0.9	39.5 ± 1.2	<.001
Induction of labor (*n* [%])	24 (77)	7 (6)	<.001
Birthweight (g) (mean ± SD)	2301 ± 247	2594 ± 213	<.001
Operative vaginal rate *n* [%]	5 (16)	26 (22)	.14
Operative vaginal for nonreassuring fetal status (*n* [%])	2 (6)	22 (18)	.11
Cesarean section rate (*n* [%])	8 (26)	23 (19)	.70
Cesarean section for nonreassuring fetal status (*n* [%])	1 (37)	17 (14)	.12
Operative delivery for nonreassuring fetal status	3 (10%)	39 (33)	.01
Admission to neonatal intensive care unit (*n* [%])	5 (16)	26 (22)	.26

performed because of ultrasound antenatal diagnosis of SGA (38%) whereas in the AGA group 96% had an induction indicated by gestational age or term prelabor rupture of membranes.

SGA babies were associated with a higher rate of cesarean sections for nonreassuring fetal status [18/151 (12%) versus 8/1202 (1%), $p < .001$], higher rate of operative vaginal deliveries for nonreassuring fetal status [24/151 (16%) versus 12/1202 (1%), $p < .001$] and higher rate of admissions to neonatal intensive care unit (NICU) [16/151 (11%) versus 18/1202 (1%), $p < .001$] compared to AGA (Table 1).

Within SGA group ($n = 151$) 21% of babies (31/151) had been antepartum detected by ultrasound. Antenatal detection was associated with lower gestational age at delivery (37.8 versus 39.5 weeks, $p < .001$), more inductions of labor (24/31 versus 7/120, $p < .001$), lower mean birthweight (2301 versus 2594 g, $p < .001$) and lower rates of operative deliveries for nonreassuring fetal status (3/31 versus 39/120, $p = .01$) compared to undetected SGA (Table 2).

Discussion

We present a retrospective study, comparing obstetric and neonatal outcomes of SGA and AGA in low-risk term pregnancies. SGA group had more nulliparous women, more inductions of labor and lower gestational age at delivery, which may have contributed to the higher risk of cesarean delivery for nonreassuring fetal status compared to AGA group. Low-risk nulliparous women have higher cesarean delivery rates than multiparous with no previous uterine scar; induction of labor and lower gestational age may be associated with an unfavorable cervix (data not included in the study) that may also be associated with higher rates of cesarean sections [13,14]. Moreover, SGA were associated with higher cesarean and operative vaginal deliveries for nonreassuring fetal status and higher rate of admissions to NICU compared to AGA. This higher rate of obstetric intervention for nonreassuring fetal status in SGA group may be due to the fact that these fetuses had a lower placental reserve near term, making them unable to overcome the demands during labor. The higher rate of admissions to NICU for SGA than AGA may also be an evidence of the lower placental reserve of these fetuses.

Since this retrospective study describes the outcomes of low-risk term pregnancies in one year we could not address less frequent outcomes such as the risk of stillbirth and neonatal mortality. Nonetheless, Mendez-Figueroa et al. recently published a multicentric analysis of 50,011 uncomplicated term pregnancies and they concluded that SGA compared to AGA babies have a significantly higher likelihood of composite neonatal morbidity, stillbirth, and neonatal mortality [1,15].

There is no consensus that third trimester ultrasound screening of SGA in low-risk pregnancies improves maternal and fetal outcomes over clinical evaluation alone. Systematic reviews recommend as a standard of care only performing a third trimester ultrasound in low-risk pregnancies with a significant lag of the symphysis-fundus distance on physical examination [16]. In accordance to this, the American College of Obstetricians and Gynecologists (ACOG) recommends that if SGA is clinically suspected we should do an ultrasound for an EFW [17]. The low accuracy of clinical evaluation for screening of SGA relies on its low sensitivity and high interobserver variation. Furthermore, symphysis-fundus distance performs better for detecting SGA as gestational age increases, making it a less valuable tool far from delivery [18].

We did a secondary analysis of the 151 cases of SGA and compared antenatal detection with undetected SGA. Using the criterion described above we verified a detection rate of SGA of 21%. Recently, the ROUTE study, an open-label parallel randomized trial, showed that SGA detection rate was superior at

36 versus 32 weeks' gestation (sensitivity, 38.8% versus 22.5%; $p = .006$). In cases of severe SGA (<3rd centile), detection rate was superior at 36 versus 32 weeks' gestation (61.4% versus 32.5%; $p = .008$) [19].

In our sample of 151 SGA babies from low-risk pregnancies, the antenatally detected group had lower gestational age at delivery and lower birthweight compared to AGA, which was probably due to more inductions of labor decided because of the diagnosis of SGA. Our data is consistent with literature and though we were not able to evaluate neonatal outcomes other than admission to neonatal intensive care unit, a recent study has concluded that despite antenatally detected SGA babies having lower birthweights and lower gestational age at birth than undetected SGA, they had significantly lower mortality (6.4 versus 12.6%) than undetected SGA without a parallel increase in severe two-year neurodevelopmental, clinical, or growth morbidity [20].

We found a statistically significant association between antenatally undetected SGA and higher operative deliveries for nonreassuring fetal status. This reinforces the hypothesis that antenatal detection of SGA permits a term induction of labor and timely delivery preventing SGA fetuses to be exposed to a post-term pregnancy that might be too demanding for their placental reserve.

The retrospective design of our study did not allow collecting data on functional parameters evaluated at the third trimester ultrasound. We considered as definition of term SGA a newborn with birthweight <10th centile. Birthweight centiles were calculated using reference curves for Spanish population given the ethnic similarity to our population and the lack of local curves. Antenatal detection of these SGA babies was considered when EFW was <10th centile. In accordance to ACOG, this is the definition of fetal growth restriction [17]. Nonetheless, this definition includes two different types of fetuses: one group that is not achieving its genetic potential of growth (true FGR) and another group of fetuses that are only constitutionally SGA. Recent data suggest that additional ultrasound parameters would help to distinguish these two types of fetuses, namely decreasing the EFW percentile cut off to <3rd centile prevents inclusion of a large number of constitutionally SGA since several studies have reinforced that the fetuses with EFW <3rd centile are the ones with the worst neonatal outcomes [21]. In our series, birthweight was also inversely associated with admission to NICU and operative deliveries for nonreassuring fetal status.

In fetuses with 3rd centile < EPF <10th centile, inclusion of functional data, in particular, umbilical artery and middle cerebral artery pulsatility index would contribute to identify true FGR [22–24]. Cerebroplacental ratio (CPR) is an independent predictor of perinatal mortality. Studies have shown that even for AGA fetuses, an abnormal CPR is associated to higher incidence of adverse outcomes [25]. It is hypothesized that these fetuses had a higher genetic growth potential and CPR may demonstrate these growth decelerations. However, further studies are needed in order to understand if it is worth to consider a routine measurement in the third trimester of low-risk pregnancies.

We acknowledge the design of the study as a major limitation since it is a retrospective study based on revision of medical records and we cannot disclose the possibility of misclassification of the outcomes and uncertain validity of the data obtained from the medical records. Nevertheless, we made an effort to compare demographic characteristics between groups, especially possible confounders associated with the higher cesarean and operative vaginal deliveries for nonreassuring fetal status on SGA compared to AGA. However, there are other variables that were not systematically registered in the medical records such as body mass index, smoking, social and economic status and that could have been potential confounders as well. Furthermore, the data presented represents a sample of a single institution in Portugal so cannot be directly generalized to other populations.

A large multicenter trial is warranted to determine if a better detection of SGA among low-risk pregnancies can improve maternal and fetal outcomes, without disproportionate interventions and iatrogenic morbidity. In conclusion, in our series of low-risk term pregnancies, SGA babies had higher operative deliveries for nonreassuring fetal status than AGA and were also more frequently admitted to NICU.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

This work was supported by a Research Grant from Fundação para a Ciência e Tecnologia (FCT) – SFRH/SINTD/92997/2013.

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Received: 14 April 2017 | Revised: 25 July 2017 | Accepted: 27 September 2017 | First published online: 31 October 2017

DOI: 10.1002/ijgo.12333

WILEY | International Journal of Gynecology & Obstetrics

CLINICAL ARTICLE

Obstetrics

Impact of maternal weight on the intra-observer and inter-observer reproducibility of fetal ultrasonography measurements in the third trimester

Catarina Policiano[1,*] | Jorge M. Mendes[2] | Andreia Fonseca[1] | Joana Barros[1] | Diana Martins[1] | Inês Reis[1] | Nuno Clode[1] | Luís M. Graça[3]

[1]Department of Obstetrics and Gynecology, CHLN-Hospital Universitário de Santa Maria, Lisbon, Portugal

[2]NOVAIMS, Universidade Nova de Lisboa, Lisbon, Portugal

[3]Faculdade de Medicina da Universidade de Lisboa, CAML Centro Académico de Medicina de Lisboa, Lisbon, Portugal

***Correspondence**
Catarina Policiano, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal.
Email: catarinapoliciano@gmail.com

Funding Information
Fundação para a Ciência e Tecnologia (FCT)

Abstract

Objective: To evaluate the effect of maternal weight on the intra- and inter-observer reproducibility of third-trimester ultrasonography fetal measurements.

Methods: The present prospective study, performed at a tertiary hospital, enrolled patients at between 35^{+0} weeks and 36^{+6} weeks of singleton pregnancies between January 1, 2015, and July 1, 2016. Fetal ultrasonography measurements were evaluated twice by a first observer and a third time by a second observer. Intra- and inter-observer consistency were analyzed using the Cronbach α reliability coefficient, and measurement reproducibility was compared with patients stratified by a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of below 25 or at least 25.

Results: The study included 197 patients (133 with BMI <25 and 64 with BMI ≥25). Among patients with a BMI below 25, the reliability coefficients for bi-parietal diameter, head circumference, abdominal circumference, and femur length measurements were 0.97, 0.95, 0.98, and 0.96, respectively, for intra-observer consistency, and were 0.97, 0.93, 0.98, and 0.95, respectively, for inter-observer consistency. Among patients with a BMI of at least 25, these values were 0.97, 0.96, 0.98, and 0.97, respectively, for intra-observed consistency, and 0.97, 0.94, 0.98, and 0.96, respectively, for inter-observer consistency.

Conclusion: High intra- and inter-observer reproducibility was observed for third-trimester fetal ultrasonography measurements, including for patients who were overweight.

KEYWORDS
Fetal biometry; Intra- and inter-observer reproducibility; Obesity; Third trimester ultrasound

1 | INTRODUCTION

Obesity is increasing worldwide; according to the World Health Organization,[1] more than 1.9 billion adults were overweight in 2014 and, of these, over 600 million were obese. Data from 2011–2014 from the United States National Center for Health[2] indicated that 34.4% of women aged 20–39 years were obese (body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters] ≥30). Obese patients are at increased risk of maternal and perinatal adverse events during pregnancy, with the risks increasing in line with BMI categories.[3]

Sonographic fetal weight estimation during the final weeks of the third trimester of pregnancy in low-risk pregnancies is considered the most effective method for diagnosing fetal growth restriction.

However, there is no consensus on the need for a routine third-trimester ultrasonography examination with the aim of screening for fetal growth restriction in low-risk pregnancies, and evidence has not yet demonstrated any objective advantages for maternal–fetal outcomes. Nonetheless, the ROUTE study,[4] an open-label parallel randomized trial, recently demonstrated that the detection rate for a small-for-gestational age fetus was superior at 36 weeks of pregnancy compared with 32 weeks (sensitivity: 38.8% vs 22.5%; P=0.006).

Ultrasonography examinations are technically more difficult in patients who are obese compared with those with a normal BMI.[5] Few studies have evaluated the accuracy of ultrasonography weight estimation in the third trimester in obese patients. Moreover, some studies[6,7] have suggested that the accuracy of ultrasonography estimates of fetal weight were not influenced significantly by maternal BMI whereas others[8,9] have concluded that the absolute percentage error for estimates was lower among patients of normal weight and that, consequently, maternal obesity decreased the accuracy of sonographic fetal weight estimation.

The aim of the present study was to evaluate intra- and inter-observer reproducibility of third trimester ultrasonography fetal biometric measurements and to compare it between pregnant women of normal weight and those who were overweight.

2 | MATERIALS AND METHODS

The present prospective observational cohort study was performed at the Department of Obstetrics and Gynecology, CHLN-Hospital Universitário de Santa Maria, Lisbon, Portugal, a tertiary center, and enrolled patients between January 1, 2015, and July 1, 2016. Patients presenting at the study center for scheduled appointments at between 35^{+0} and 36^{+6} weeks of a low-risk singleton pregnancy, and agreed to undergo three ultrasonography evaluations on the same day were eligible for inclusion. The presence of maternal diseases or fetal anomalies were exclusion criteria. The study was approved by the Hospital Universitário de Santa Maria local ethics committee and written informed consent was obtained for each patient before enrolment.

Maternal age at enrollment, parity, BMI, and maternal waist circumference were recorded. BMI was calculated using maternal height and weight measurements from the beginning of pregnancy; these data were collected from clinical records. Maternal waist circumference was measured at 35^{+0}–36^{+6} weeks of pregnancy to the nearest 1 mm at the midpoint between the lower ribs and the pelvic bone using a flexible tape.

The primary outcome was the reproducibility of fetal bi-parietal diameter, head circumference, abdominal circumference, and femur length ultrasonography measurements (GE Voluson E8 with a 3.5-MHz transducer; GE Healthcare, Wauwatosa, WI, USA). All measurements were made by established methods[10,11] with fetal structures of interest occupying at least 30% of the monitor. Bi-parietal diameter and head circumference were measured from axial images of the fetal brain at the transthalamic plane, with an angle of insonation as close to 90° as possible. Head measurements were performed in the transthalamic plane; evidence[12] has shown that, particularly in late pregnancy, this section plane is easier to identify and allows more reproducible measurements compared with the transventricular plane.

The head had to be oval in shape, symmetrical, and centrally positioned for taking measurements. The midline echo (representing the falx cerebri) had to be broken anteriorly, at one-third of its length, by the cavum septi pellucidi. Bi-parietal diameter was measured by outer-to-inner caliper placement at the widest part of the skull. A reproducibility study[11] has demonstrated that both outside-to-outside and outside-to-inside measurements are equivalent. The outer-to-inner technique was adopted in the present study to avoid the generation of artifacts by the distal echo of the calvarium. The measurement of the abdominal circumference was performed from a cross-sectional view of the fetal abdomen as close as possible to circular, at the level of the bifurcation of the main portal vein into the left and right branches, and with the stomach visible. Both head circumference and abdominal circumference were measured using the ellipse facility on the outer borders of the skull and of the abdomen, respectively. No manual tracing was used. Femur length was measured using a longitudinal view of the fetal thigh closest to the probe, with the femur as close as possible to the horizontal plane; measurement was performed with the full length of the bone visualized by including only the femoral diaphysis length, excluding the hypo-echogenic cartilaginous structures at either end of the femur.

Fetal biometric measurements were compared instead of using fetal weight estimates because these estimates are made by applying one of many formulae to the individual parameters and all formulae have specific margins of error of at least ±15%. Each measurement was evaluated twice by the first observer and a third time by a second observer who was masked to the first observer's measurements. There were five sonographers (C.P., A.F., J.B., D.M., and I.R.) who participated in the study; three (C.P., A.F., and J.B. were residents in the second half of their residency program, and two (D.M. and I.R.) were consultants with less than 5 years of experience.

Consensus between and among observers was analyzed using the Pearson correlation coefficient and the Cronbach α reliability coefficient. A value above 0.75 was considered to indicate reliable consensus for the coefficients. Considering that two measurements made by the same sonographer or by two different sonographers are close to a real measure (not observed in the present study), the Cronbach α coefficient was used to evaluate the reliability of the measurements. The three evaluations of the same parameter for the same patients were made at different time points but were very close to each other; the closer the measurements are to each other, the more reliable the methods. This reliability was evaluated with the Cronbach α coefficient.

The intra- and inter-observer measurements were compared within subgroups of patients based on maternal BMI; patients were grouped using BMI values below 25 or BMI values of at least 25, and comparisons were made between the groups with the paired-sample t test. In a further analysis, intra- and inter-observer measurements were compared between patients stratified by the median maternal waist circumference. Bland–Altman plots were created to determine agreement and bias between paired measurements by one observer and by two observers, respectively. If there was perfect agreement between the measurements, the difference would be zero. Measurements were considered highly reproducible if the mean difference was close to zero and there was low dispersion around zero (95% of the points of the graph between the two limits). Analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and $P<0.05$ was considered statistically significant.

3 | RESULTS

The present study enrolled 197 patients; 18 (9%) had a low BMI (<18.5), 115 (58%) had a normal BMI (≥18.5 and <25), 44 (22%) had an overweight BMI (≥25 and <30), and 20 (10%) were obese (≥30) (Table 1). It was possible to obtain all measurements for all patients by the methods described above. No incomplete ultrasonography evaluations were recorded, corresponding to a total of 591 ultrasonography measurements being made.

When patients were stratified using a BMI of under 25 or at least 25, very high intra- and inter-observer correlation coefficients and Cronbach α coefficients were recorded for both groups across all four biometric parameters (Table 2). All of them were above 0.90 for both groups, except for the head circumference inter-observer correlation coefficients; Cronbach α coefficients above 0.90 were recorded for these measurements (Table 2).

Unlike BMI, there is no standardized maternal waist circumference reference cut-off value for patients who are pregnant. In the present study cohort, the mean and median maternal waist circumference were 104.13 cm and 104 cm, respectively. A maternal waist circumference of 104 cm was chosen as the cut-off value for stratifying patients (higher maternal waist circumference [≥104 cm] and lower maternal waist circumference [<104 cm]). Similarly to stratifying patients by BMI, slightly lower measurement agreement was observed for head circumference measurement than for abdominal or femur measurements. However, all Cronbach α coefficients were above 0.90 (Table 3). Further, the mean differences between the intra- and inter-observer fetal measurements were not statistically significant for all patient groups (stratified by BMI or maternal waist circumference) (Table 4).

Bland–Altman plots were plotted for fetal bi-parietal diameter, head circumference, abdominal circumference, and femur length measurements taken by the same and different observers for all patients stratified by BMI (Figs. 1 and 2). For all parameters, mean differences were verified as close to zero with 95% of intra- and inter-observer mean differences within the limits.

TABLE 1 Demographic characteristics (n=197).[a]

Variables	Value
Maternal age, y	29.7 ± 5.5
Parity	
Nulliparous	121 (61.4)
Multiparous	76 (38.6)
BMI at beginning of pregnancy	23.8 ± 4.5
BMI group	
Low weight (<18.5)	18 (9.1)
Normal weight (≥18.5 and <25)	115 (58.4)
Excess weight (≥25 and <30)	44 (22.3)
Obese (≥30)	20 (10.2)
Maternal weight gain at ultrasonography, kg[b]	11.4 ± 4.9
Maternal waist circumference at ultrasonography, cm	104.1 ± 8.5
Pregnancy duration at ultrasonography, wk	36

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a]Values are given as mean ± SD, number (percentage), or median.
[b]Compared with pre-pregnancy weight.

TABLE 2 Intra- and inter-observer correlation and reliability of fetal ultrasonography biometric measurements, stratified by early-pregnancy BMI.

	Intra-observer reliability		Inter-observer reliability	
Parameter	Pearson correlation coefficient (95% CI)	Cronbach α reliability coefficient	Pearson correlation coefficient (95% CI)	Cronbach α reliability coefficient
BMI <25				
BPD	0.94 (0.92–0.96)	0.97	0.94 (0.92–0.96)	0.97
HC	0.91 (0.88–0.94)	0.95	0.87 (0.82–0.90)	0.93
AC	0.96 (0.95–0.97)	0.98	0.97 (0.95–0.98)	0.98
FL	0.92 (0.89–0.92)	0.96	0.91 (0.87–0.93)	0.95
BMI ≥25				
BPD	0.94 (0.91–0.97)	0.97	0.95 (0.91–0.97)	0.97
HC	0.93 (0.89–0.96)	0.96	0.89 (0.82–0.93)	0.94
AC	0.96 (0.93–0.98)	0.98	0.97 (0.95–0.98)	0.98
FL	0.94 (0.90–0.96)	0.97	0.92 (0.87–0.95)	0.96

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; BPD, bi-parietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

4 | DISCUSSION

The present prospective observational cohort study evaluated the reproducibility of fetal biometric measurements among patients at 35^{+0} to 36^{+6} weeks of pregnancy. The four most commonly used fetal measurements (bi-parietal diameter, head circumference, abdominal circumference, and femur length) demonstrated excellent intra- and inter-observer agreement, including for patients who were overweight.

Evidence from randomized trials and meta-analyses has failed to demonstrate that a routine third-trimester screening for fetal growth restriction among low-risk pregnancies improves maternal and fetal outcomes compared with clinical evaluation alone.[5] It could be argued that the results of these studies have limited contemporary validity owing to the use of outdated surrogates for fetal growth,

TABLE 3 Intra- and inter-observer correlation and reliability of fetal ultrasonography biometric measurements, stratified by maternal waist circumference at ultrasonography.

Parameter	Intra-observer reliability: Pearson correlation coefficient (95% CI)	Intra-observer reliability: Cronbach α reliability coefficient	Inter-observer reliability: Pearson correlation coefficient (95% CI)	Inter-observer reliability: Cronbach α reliability coefficient
Maternal waist circumference <104 cm				
BPD	0.94 (0.91–0.96)	0.97	0.93 (0.90–0.95)	0.96
HC	0.89 (0.84–0.93)	0.94	0.88 (0.82–0.92)	0.93
AC	0.94 (0.92–0.96)	0.97	0.95 (0.93–0.97)	0.98
FL	0.93 (0.90–0.95)	0.97	0.90 (0.86–0.94)	0.95
Maternal waist circumference ≥104 cm				
BPD	0.94 (0.91–0.96)	0.97	0.95 (0.92–0.96)	0.97
HC	0.93 (0.90–0.95)	0.97	0.85 (0.78–0.90)	0.92
AC	0.97 (0.95–0.98)	0.98	0.97 (0.96–0.98)	0.99
FL	0.92 (0.89–0.95)	0.97	0.92 (0.88–0.94)	0.96

Abbreviations: CI, confidence interval; BPD, bi-parietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

and older ultrasonography equipment or protocols, where diagnosis of fetal growth restriction elicited no change in patient management. Nonetheless, in the absence of a third-trimester ultrasonography examination, undetected fetal growth restriction could result in a fetus having insufficient placental reserve to withstand pregnancy up to 41 weeks and the demands of labor at that gestational age; this could result in an increase in adverse obstetric outcomes. Moreover, contrary to early-onset fetal growth restriction, where the major challenge is management, the major challenge for late fetal growth restriction is diagnosis because a mature fetus has a lower tolerance to hypoxia and a very short period for identification.[13] Given these contradictory hypotheses, more research on the usefulness and accuracy of a routine third-trimester ultrasonography in low-risk pregnancies is warranted. In accordance with recent data suggesting that the detection of fetal growth restriction was superior at 36 weeks of pregnancy compared with 32 weeks,[4] the present study assessed the intra- and inter-observer reproducibility of biometric measurements at 35^{+0} to 36^{+6} weeks of pregnancy. Moreover, there is also controversy regarding the accuracy of ultrasonography fetal weight estimates in the third trimester in patients with high BMI in comparison with those with lower BMI; in the present study, the reproducibility of ultrasonography parameters was assessed among patients of different BMI groups in an attempt to validate third-trimester ultrasonography assessment in this population.

TABLE 4 Mean differences in intra-observer and inter-observer biometric measurement.

Comparison groups	Comparison of mean differences (*P* value)[a]: BPD	HC	AC	FL
Intra-observer difference for patients with BMI <25	0.10	0.23	0.89	0.11
Intra-observer difference for patients with BMI ≥25	0.82	0.96	0.48	0.65
Inter-observer difference for patients with BMI <25	0.21	0.21	0.33	0.33
Inter-observer difference for patients with BMI ≥25	0.72	0.59	0.26	0.48
Intra-observer difference for patients with MWC <104 cm	0.16	0.13	0.75	0.17
Intra-observer difference for patients with MWC ≥104 cm	0.45	0.81	0.28	0.38
Inter-observer difference for patients with MWC <104 cm	0.25	0.77	0.37	0.12
Inter-observer difference for patients with MWC ≥104 cm	0.96	0.45	0.47	0.86

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BPD, bi-parietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; MWC, maternal waist circumference.

[a]Paired-ample *t* test.

Despite several studies having evaluated the mean error among fetal weight estimates from third trimester ultrasonography,[7–9] the present study was, to the best of our knowledge, the first to evaluate the reproducibility of third-trimester fetal biometric ultrasonography measurements among patients with high BMI compared with patients with normal BMI. A previous study[14] did evaluate the reproducibility of ultrasonography measurements in a cohort of patients with a wide range of pregnancy durations. Previous studies have reported that the accuracy of ultrasonography decreases gradually as pregnancy length increase, and that this deterioration is higher at increased BMI.[8,15] The present study had the advantage of restricting the analyses to a small pregnancy-length interval. At 35^{+0} to 36^{+6} weeks of pregnancy, high intra- and inter-sonographer accuracy was demonstrated, with correlation coefficients above 0.9 for almost all biometric parameters, independent of maternal weight and abdominal circumference. Coefficients of 0.8–0.9 were only obtained for head measurements; this can be explained through the presence of technical challenges when performing ultrasonography examinations during the late third

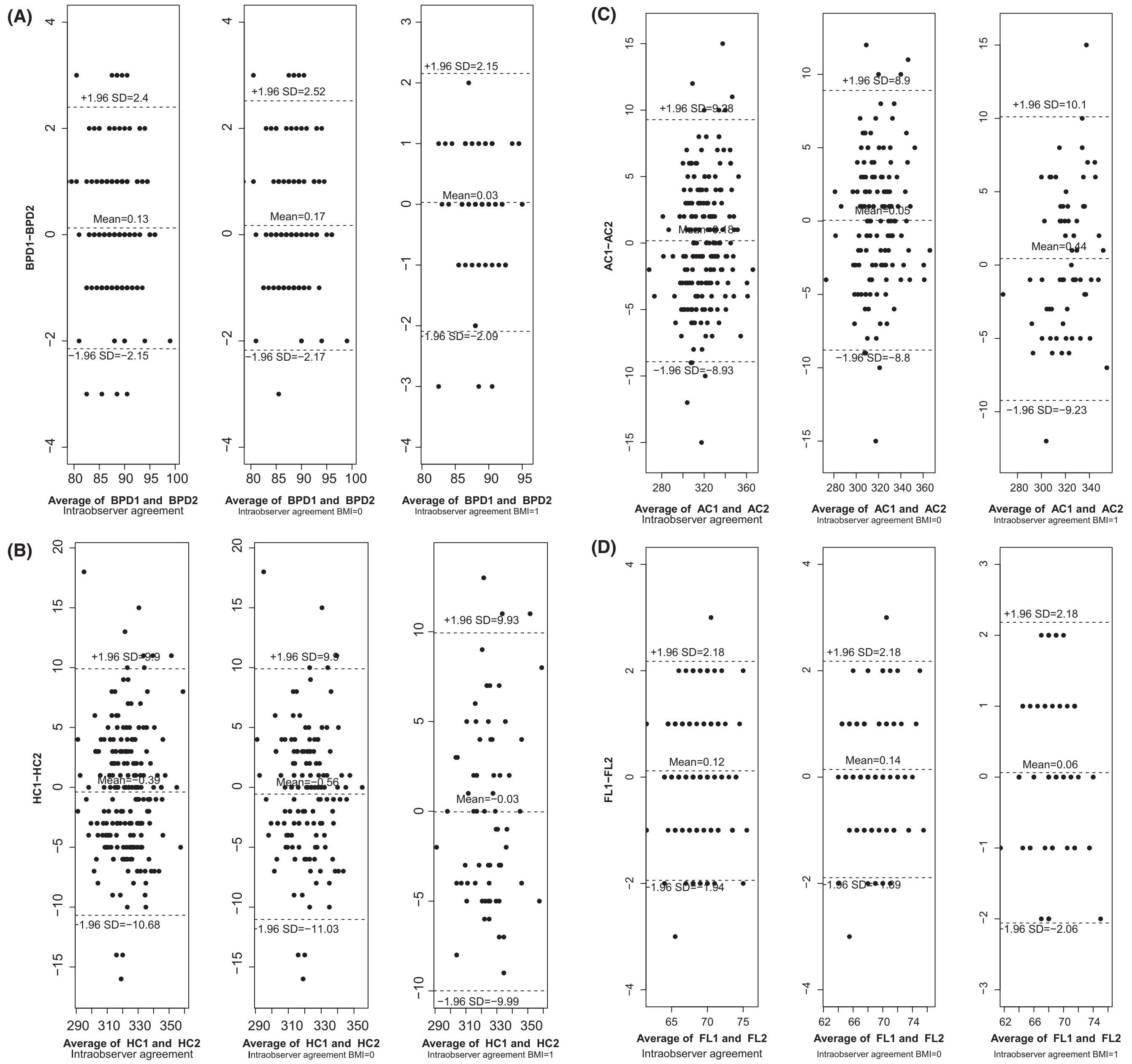

FIGURE 1 Bland–Altman plots of the mean difference (with 95% limits) in BPD (A), HC (B), AC (C), and FL (D) measurements performed by the same operator. BMI=0 indicates patients with BMI <25, and BMI=1 indicates patients with BMI ≥25. Abbreviations: BPD, bi-parietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; BMI, body mass index (weight in kilograms divided by the square of height in meters).

trimester, such as the fetal head lying low in the pelvis and less amniotic fluid. Both of these circumstances may make it more difficult to obtain perfect imaging planes for the fetal head. Nonetheless, these correlation coefficients further reinforce the high reliability of ultrasonography measurements.

It has been suggested[16] that a thicker maternal abdominal wall is associated with reduced feasibility of completing an ultrasonography examination in a pregnant patient who is obese, and with poor image quality. The absorption of ultrasonography waves by subcutaneous fat makes ultrasonography more difficult.[17] Maternal waist circumference could be an indicator of higher abdominal wall thickness and fat. Recently, it was reported that maternal waist circumference could be predictive of fetal weight estimation failure, and 105 cm was defined as an optimal cut-off value with 70% sensitivity and 61% specificity.[18] Nonetheless, it is concluded here that fetal biometric measurements were highly reproducible in both patients with higher and lower maternal abdominal waist circumferences.

In accordance with other studies that have reported good accuracy with ultrasonography performed by residents and inexperienced operators,[19,20] high reliability was observed in the present study for fetal measurements performed by non-experienced sonographers.

It is acknowledged that including both patients of excess weight and those who were obese in the same group was a limitation of the present study. Further, the number of women in the obese category

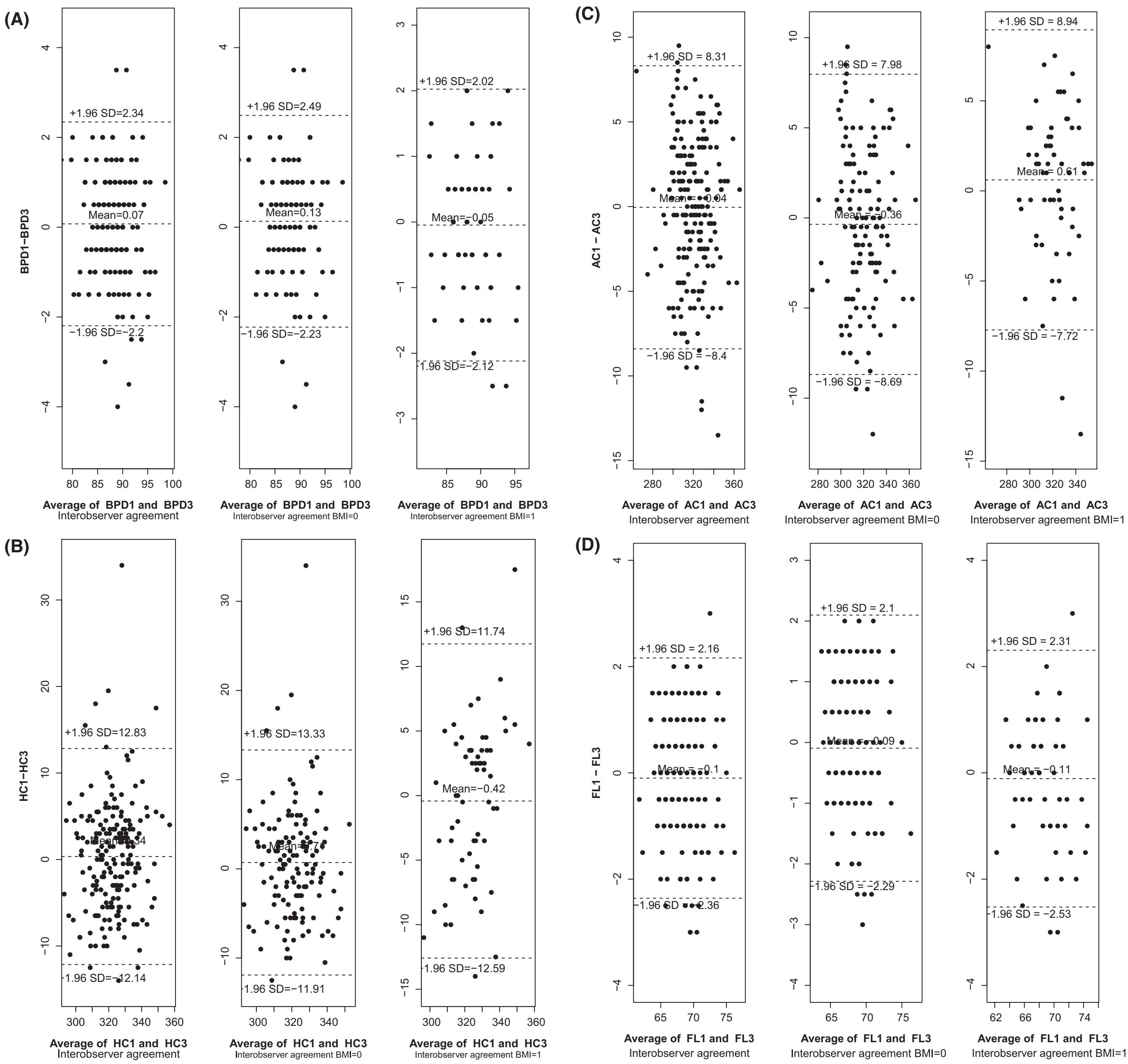

FIGURE 2 Bland–Altman plots of the mean difference (with 95% limits) in BPD (A), HC (B), AC (C), and FL (D) measurements performed by the two different operators. BMI=0 indicates patients with BMI <25, and BMI=1 indicates patients with BMI ≥25. Abbreviations: BPD, bi-parietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; BMI, body mass index (weight in kilograms divided by the square of height in meters).

was small; this prevented a deeper analysis of the impact of obesity on the reproducibility of ultrasonography measurements. Ideally, with a larger sample size, patients in the high BMI group would have been stratified into two groups, isolating patients with obesity; this would increase the power of the results. Nevertheless, the primary aim was to compare the accuracy of fetal ultrasonography measurements in patients of normal weight with those who were overweight. The present study did not intend to evaluate the technical difficulty of performing ultrasonography evaluations in the present cohort. In an attempt to do so, it would be interesting, as a future line of research, to evaluate the intra- and inter-observer quality of the images obtained for both groups.

In conclusion, the present study demonstrated high intra- and inter-observer reproducibility of third-trimester fetal ultrasonography biometric measurements, including among patients who were overweight.

AUTHOR CONTRIBUTIONS

CP contributed to the conception of the study, the design of the study, data collection and analysis, and manuscript writing. JMM contributed to data analysis and manuscript writing. AF, JB, DM, and IR contributed to data collection and revising the manuscript. NC and LMG contributed to the design of the study and revising the manuscript.

ACKNOWLEDGMENTS

The present study was supported by a Research Grant from the Fundação para a Ciência e Tecnologia (FCT) SFRH/SINTD/92997/2013.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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European Journal of Obstetrics & Gynecology and Reproductive Biology 240 (2019) 187–191

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

National-survey for evaluation of the best screening method of late fetal growth restriction in low risk pregnancy: A prospective study

Catarina Policiano[a,*], Catarina Reis-de-Carvalho[a], Nuno Clode[a], Luís Mendes Graça[b]

[a] Department of Obstetrics and Gynecology, CHLN-Hospital Universitário de Santa Maria, Lisbon, Portugal
[b] Faculdade de Medicina da Universidadade de Lisboa, Lisbon, Portugal

ARTICLE INFO

Article history:
Received 13 May 2019
Received in revised form 2 July 2019
Accepted 8 July 2019
Available online xxx

Keywords:
Fetal growth restriction
Ultrasound screening
Third trimester
Low risk pregnancies
Opinion of physicians

ABSTRACT

Objective: To compare knowledge and practices surrounding third trimester screening of fetal growth restriction (FGR) in low risk pregnancies among Portuguese Gynecologists/Obstetricians (GOs) and General Practitioners (GPs). Primary outcome was to compare the proportion of GOs that consider the need of a third trimester ultrasound (estimation of fetal weight) for screening of FGR in low risk pregnancies and the best time to perform it with the corresponding proportion of GPs.
Study design: We have conducted a prospective, observational cohort study based on application of surveys to GOs and GPs. Questionnaires were sent by e-mail to physicians and they filled them online. A second reminder e-mail was sent 7 days later. Recruitment was also done personally at scientific meetings. A total of 573 surveys were available for analysis, 298 corresponded to GOs and 275 to GPs. We used χ^2 test to compare dichotomous variables and Kruskal-Wallis test for the comparison of ordinal variables. *P* values <0.05 were considered statistically significant.
Results: The vast majority of GOs and GPs (93%) considered that third trimester ultrasound is useful and needed for surveillance of low risk pregnancy. A higher proportion of GOs (38%) selected 35th–37th weeks as the best time to perform the ultrasound compared to GPs (10%) ($p < 0.001$). GOs (51%) consider that symphysis-fundus distance is a measurement with moderate accuracy for screening of FGR while GPs (61%) attribute a low accuracy ($p < 0.001$). Fifty percent (50%) of GOs consider that performing a third trimester ultrasound will have no impact on cesarean delivery rate for fetal distress, while 41% of GPs consider that routine ultrasound will contribute to increase this rate ($p < 0.001$). The majority of GPs (52%) consider that routine ultrasound will contribute to diminish the admission rate to neonatal intensive care unit while GOs revealed a dichotomy with 43% of respondents reporting that it will diminish the rate and 40% that it will have no impact.
Conclusion: Varied opinions among the clinicians included in our sample reflect the controversy that remains on the best screening of FGR in low risk pregnancies.

1 Introduction

Death of a growth-restricted fetus is the second most common etiology of stillbirth [1,2]. Fetal growth restriction (FGR) without prenatal diagnosis is associated with higher risk of adverse neonatal outcomes compared with FGR whose diagnosis was made antepartum. Moreover, a significant proportion of term stillbirths correspond to undiagnosed FGR [3,4]. The most commonly used clinical screening tool in this population is the serial measurement of symphysis-fundus distance, which is a method of variable and low sensitivity [5,6]. Sonographic fetal weight estimation (EFW) at the last weeks of third trimester in low-risk pregnancies is an effective method for diagnosis of FGR permitting close surveillance and timely delivery [7]. Evidence from meta-analysis has failed to demonstrate any real benefit from routine third-trimester screening for FGR in low risk pregnancies [8]. It may be argued that the results of these studies have limited contemporary validity as they have used outdated surrogates of fetal growth or protocols in which FGR diagnosis elicited no change in management. The main argument against a routine third trimester ultrasound is the possibility that it could induce over diagnosis of FGR since a significant proportion of these fetuses are constitutively small for gestational age (SGA). These are not pathological fetuses but it is very difficult to distinguish them and they would be put at risk of unnecessary obstetric intervention, iatrogenic preterm deliveries, labor induction and eventually more

* Corresponding author at: Av. Prof. Egas Moniz, 1649-035, Lisboa, Portugal.
E-mail address: catarinapoliciano@gmail.com (C. Policiano).

https://doi.org/10.1016/j.ejogrb.2019.07.009
0301-2115/

cesarean deliveries. On the other hand, in the absence of third trimester ultrasound, undetected FGR may not have enough placental respiratory reserve to withstand pregnancy up to 41 weeks and the demands of labor at that gestational age which would result in higher cesarean deliveries and potentially more admissions to neonatal intensive care unit (NICU).

In Portugal, in accordance with guidelines of *Direcção Geral de Saúde (DGS)* from 2015, FGR screening in low risk pregnancies is performed with an ultrasound for EFW at 30th–33rd weeks [9]. Nonetheless, recent data from *ROUTE study*, an open-label parallel randomized trial, showed that FGR detection rate was superior at 36 *vs* 32 weeks' gestation (sensitivity, 38.8% *vs* 22.5%; $p = 0.006$) [10].

Gynecologists/Obstetricians (GOs) and General Practitioners (GPs) are in a unique position to screen for FGR. Given the adverse outcomes associated with missed FGR and the importance to optimize screening, our aim was to investigate knowledge and practices surrounding screening of FGR in low risk pregnancies among Portuguese GOs and GPs.

2 Materials and methods

We have conducted a prospective cohort study based on application of surveys to GOs and GPs. Questionnaires were sent by e-mail to physicians and they filled them online. A second reminder e-mail was sent 7 days later. We had the approval of National Scientific Societies in order to distribute the questionnaires. When physicians register on scientific societies with their e-mails, they give permission to receive e-mails and no ethics committee or informed consent was required for this study. Questionnaires were announced by social media such as medical groups on facebook. Recruitment was also done personally at scientific meetings. The questionnaires were completely anonymous.

In accordance to National Statistics, there are 1772 GOs and 7149 GPs registered in Portugal as of 2018. All that have access to e-mail and/or attend scientific meetings were eligible to fill the survey.

The survey included questions about physician demographics, training and practice characteristics. Responses were therefore assumed to refer to a respondent's self-reported current practices about the screening of FGR, offering a cross-sectional view.

Primary outcome was to compare the proportion of GOs that consider the need of a third trimester ultrasound (EFW) for FGR screening in low risk pregnancies and the best time to perform it with the corresponding proportion of GPs.

Secondary outcomes included: to compare the opinion of GOs and GPs regarding accuracy of symphysis-fundus distance for screening of FGR in low risk pregnancies and also about the impact of a routine third trimester ultrasound on cesarean delivery rate for fetal distress and on admission of newborns to NICU.

We did subgroup analysis of the endpoints described above based on current weekly activity (surveillance of low risk pregnancy and/or performing obstetric ultrasound). With this analysis, we expected to evaluate if there were differences in the knowledge of physicians who deal regularly with the diagnosis, management and consequences of FGR in low risk pregnancies compared with those that do not have this current practice. All this data was included in preliminary questions at the beginning of the survey. It was made in multiple-choice format and took less than 5 min to complete.

Statistical analysis was performed with STATA 14.2. χ^2 test was used to compare categorical variables. Comparison of ordinal variables was performed with Kruskal-Wallis test. For these variables, we considered the following hypotheses: null (0%), low (<10%), moderate (10–90%), high (>90%). *P* values <0.05 were considered statistically significant.

As far as we know there is no study comparing the opinion of physicians regarding FGR screening. Since we had no data to base on our expected difference between groups in order to estimate sample size, we decided to use the total of physicians included in this study that were registered at National Medical Council. We may hypothesize that physicians are used to national guidelines and that around 75% of GPs will consider that 30th–33rd weeks is the best time to perform it, leaving about 25% who would select 35th–37th weeks. Recent evidence has been highly debated in scientific meetings of GOs and we may consider that these physicians might be more aware of this with a higher proportion selecting 35th–37th weeks.

In our baseline population, we have a ratio of GPs/GOs of 4.03 (7149/1772). Considering a response rate of 20%, we would include 1430 GPs ($N1 = 7149 \times 0.20$) and 354 GOs ($N2 = 1772 \times 0.20$), with $N1/N2 = 4.03$. Given that around 25% of GPs would choose 35^{th}-37^{th} weeks, for a total sample size of 1784 (N1 + N2), with a significance α level of 0.05 and 80% power, we would expect to be able to detect a difference of 8% between the proportions of GPs and GOs that would select 35^{th}-37^{th} weeks as the best time to perform the ultrasound.

3 Results

A total of 573 surveys were available for analysis, 298 corresponded to GOs and 275 to GPs, with a response rate of 17% and 4%, respectively. Demographic characteristics are described in Table 1. Respondents had been in practice for a median of 6 years (IQR 2;15).

The vast majority of GOs and GPs (93%) considered that third trimester ultrasound is useful and needed for surveillance of low risk pregnancy (Table 2). GPs are very consistent regarding the best time to perform third trimester ultrasound, with 90% defending 30^{th}-33^{rd} weeks. Among GOs, 38% consider that the best time to perform third trimester screening is 35^{th}-37^{th} weeks ($p < 0.001$).

Table 1
Demographic characteristics of GOs and GPs respondents.

Variables	Gynecologists/Obstetricians (n = 298)	General Practitioners (n = 275)	*p* value
Age (years) [median (IQR)]	34 (30;45)	32 (29;36)	<0.001
Sex (n [%])			0.98
Female	257 (86.2)	237 (86.2)	
Male	41 (13.8)	38 (13.8)	
Position (n [%])			0.97
Resident	124 (41.6)	114 (41.5)	
Consultant	174 (58.4)	161 (58.5)	
Performs weekly surveillance of low risk pregnancy (n [%])	220 (73.8)	251 (91.3)	<0.001
Performs weekly obstetric ultrasound (n [%])	154 (51.7)	18 (6.5)	<0.001

GOs - Gynecologists/Obstetricians; GPs - General Practitioners; IQR - interquartile range.

Table 2
Opinion of GOs and GPs regarding FGR screening during third trimester in low risk pregnancies.

Variables	Gynecologists/Obstetricians (n = 298)	General Practitioners (n = 275)	*p* value
Accuracy of symphysis-fundus distance in detection of FGR			*<0.001*
Null (0%)	20 (6.7)	11 (4.0)	
Low (<10%)	119 (39.9)	167 (60.7)	
Moderate (10–90%)	151 (50.7)	92 (33.5)	
High (>90%)	8 (2.7)	5 (1.8)	
Considers that routine third trimester ultrasound is needed	276 (92.6)	256 (93.1)	0.83
Best time to perform third trimester ultrasound			< 0.001
30^{th}-33^{rd} weeks	172 (62.3)	230 (89.8)	
35^{th}-37^{th} weeks	104 (37.7)	26 (10.2)	
Impact of third trimester ultrasound on cesarean deliveries			<0.001
Decrease	51 (17.1)	92 (33.5)	
Null	149 (50.0)	71 (25.8)	
Increase	98 (32.9)	112 (40.7)	
Impact of third trimester ultrasound on NICU admissions			0.04
Decrease	127 (42.6)	143 (52.0)	
Null	118 (39.6)	80 (29.1)	
Increase	53 (17.8)	52 (18.9)	

GOs - Gynecologists/Obstetricians; GPs - General Practitioners; FGR - fetal growth restriction; NICU - neonatal intensive care unit.

Regarding clinical screening of FGR with symphysis-fundus distance, GOs and GPs have different opinions (Table 2). GOs (51%) consider that symphysis-fundus distance is a measurement with moderate accuracy for screening of FGR while GPs (61%) attribute a low accuracy ($p < 0.001$). Less than 5% of all physicians consider that symphysis-fundus distance is a measurement of high accuracy.

GOs and GPs also have different opinions about the impact of routine third trimester ultrasound on cesarean delivery rate for fetal distress. Fifty percent (50%) of GOs consider it will have no impact on cesarean delivery rate for fetal distress, while 41% of GPs consider that it will contribute to increase this rate ($p < 0.001$). Opinions also diverge regarding the impact on admissions of newborns to NICU ($p = 0.04$). The majority of GPs (52%) consider that it will contribute to diminish admissions to NICU while GOs revealed a dichotomy with 43% of respondents reporting that it will diminish the rate and 40% that it will have no impact.

Responses to questions regarding third trimester FGR screening were stratified based on current clinical activity. Eighty-two percent 82% (471/573) of physicians performed weekly surveillance of low risk pregnancies and 30% (172/573) performed weekly obstetric ultrasound.

Symphysis-fundus distance was a measurement with low to moderate accuracy for screening of FGR for both groups of physicians that perform weekly surveillance of low risk pregnancies (n = 471) and the ones that do not have this activity (n = 102). Most of physicians in both groups acknowledge the usefulness of routine third trimester ultrasound. There was no statistically significant difference between groups regarding the best time to perform the ultrasound, the impact of routine third trimester ultrasound on the rate of cesarean deliveries and admissions to NICU (Table 3).

Comparing the group of physicians that perform weekly obstetric ultrasound (n = 172) with the ones that do not perform scans (n = 401), both consider that symphysis-fundus distance is a measurement with low to moderate accuracy for FGR screening. A higher proportion of physicians that perform obstetric ultrasound consider that the best time to perform the ultrasound is 35^{th}-37^{th} weeks, compared with physicians that do not perform obstetric ultrasound (39% *vs* 19%, $p < 0.001$). Forty-five percent (45%) of physicians that perform obstetric ultrasound consider that third trimester scan will have no impact on cesarean delivery rate for fetal distress while 39% of the ones that do not perform scans

Table 3
Opinion of physicians regarding FGR screening during third trimester in low risk pregnancies according to clinical activity.

Variables	Surveillance of low risk pregnancies		*p* value	Perform obstetric ultrasound		*p* value
	Yes (471)	No (102)		Yes (172)	No (401)	
Accuracy of symphysis-fundus distance in detection of FGR			0.94			0.67
Null (0%)	24 (5.1)	7 (6.9)		14 (8.1)	17 (4.2)	
Low (<10%)	238 (50.5)	48 (47.1)		75 (43.6)	211 (52.6)	
Moderate (10-90%)	198 (42.0)	45 (44.1)		80 (46.5)	163 (40.7)	
High (>90%)	11 (2.4)	2 (1.9)		3 (1.8)	10 (2.5)	
Considers that routine third trimester ultrasound is needed	440 (93.4)	92 (90.2)	0.25	158 (91.9)	374 (93.3)	0.55
Best time to perform third trimester ultrasound			0.09			<0.001
30th–33rd weeks	337 (76.6)	63 (68.5)		97 (61.4)	303 (81.0)	
35th–37th weeks	103 (23.4)	29 (31.5)		61 (38.6)	71 (19.0)	
Impact of third trimester ultrasound on cesarean deliveries			0.37			0.03
Decrease	129 (27.4)	14 (13.7)		39 (22.7)	104 (25.9)	
Null	171 (36.3)	48 (47.1)		78 (45.3)	141 (35.2)	
Increase	171 (36.3)	40 (39.2)		55 (32.0)	156 (38.9)	
Impact of third trimester ultrasound on NICU admissions			0.26			0.13
Decrease	235 (49.9)	35 (34.3)		82 (47.7)	188 (46.9)	
Null	153 (32.5)	45 (44.1)		65 (37.8)	133 (33.2)	
Increase	83 (17.6)	22 (21.6)		25 (14.5)	80 (19.9)	

GOs - Gynecologists/Obstetricians; GPs - General Practitioners; FGR - fetal growth restriction; NICU - neonatal intensive care unit.

consider that it will contribute to decrease this rate (p = 0.03). Both groups have similar proportions regarding the potential impact of third trimester ultrasound to decrease the rate admissions to NICU (Table 3).

4 Comment

The best screening of late FGR in low risk pregnancies has received emphasis over time and still remains to be defined. Nearly 93% of respondents consider that routine third trimester ultrasound is needed. This high percentage is probably due to the fact that national guidelines recommend third trimester ultrasound. Although meta-analysis has failed to demonstrate any real benefit from routine third-trimester ultrasound, the World Health Organization has recently recommended that it might be useful when performed as an antenatal screening to detect fetal compromise and predict complications in apparently healthy pregnancies [11].

Few respondents (less than 5%) consider that symphysis-fundus distance is a measurement with high accuracy. The different opinion of GOs and GPs is consistent with literature that attributes a variable sensitivity to this type of screening, probably because the measurement is not always properly performed and there are limitations associated with maternal characteristics [5,6]. A prospective outcome study indicated that universal third trimester ultrasound almost tripled the detection of SGA babies compared with clinically indicated sonography with serial measurement of symphysis-fundus distance (57% *vs*. 20%) [12].

Results from this survey reinforce that, where there are unclear or conflicting recommendations, there are varied and conflicting practices among clinicians. Regarding the best time to perform third trimester ultrasound, a higher proportion of GOs (38%) selected 35th–37th weeks the best time to perform the ultrasound compared to GPs (10%). This difference may be due to the fact that GOs discuss more frequently this topic at scientific meetings and may be more familiar with recent studies that suggest that an ultrasound after 35 weeks has a higher detection rate of FGR compared with an earlier ultrasound during third trimester [10,13].

GOs mainly considered that third trimester ultrasound will have no impact on cesarean delivery rate for fetal distress, probably because they think that detection of FGR will include two groups of fetuses: a group of FGR that will be timely delivered and probably will avoid later emergent cesarean sections and another proportion of constitutionally small fetuses that could induce iatrogenic obstetric intervention. Similarly, 40% of GOs consider that third trimester ultrasound will have no impact on admissions to NICU, while 43% considered that it could reduce this rate. This last group may suggest that the ultrasound could help selecting more appropriate surveillance and timely delivery for detected FGR with lower morbidity.

In a prior retrospective study, our group analyzed 1429 term low risk pregnancies and concluded that SGA term babies (EFW < 10th percentile) had a statistically significant higher rate of cesarean deliveries for intrapartum fetal distress than appropriate for gestational age (18/151 *vs.* 8/1202, $p<0.001$) as well as a higher rate of admissions to NICU (16/151 *vs.* 18/1202, $p<0.001$) [14]. Antepartum detection of SGA neonates showed a statistically lower rate of operative deliveries for nonreassuring fetal status than undetected group (3/31 *versus* 39/120, p = .01) [14]. In our sample, 30^{th}-33^{rd} weeks ultrasound only detected 36% of SGA neonates and antepartum detection of FGR was associated with better outcome. Other groups have found that among uncomplicated term pregnancies, small- compared to appropriate-for-gestational-age newborns have a significantly higher likelihood of adverse outcomes [15–17].

GPs mainly considered that a routine third trimester ultrasound will contribute to increase cesarean rate for fetal distress and will decrease the admissions to NICU. Although we did not ask physicians the reasons that justify these choices, we can hypothesize that GPs may have the idea that in case of ultrasound detected FGR, these fetuses may need to be delivered by cesarean section and this would be protective of adverse outcome. Nonetheless, evidence has demonstrated that planned cesarean deliveries are associated with more NICU admissions compared to planned vaginal deliveries [18].

In our subgroup analysis, physicians that perform obstetric ultrasound more frequently selected 35^{th}-37^{th} weeks as the best time to perform the ultrasound compared to physicians that do not perform obstetric ultrasound. Physicians that perform ultrasound may be more updated in terms of recent literature that has attributed a higher detection rate of FGR to a later ultrasound during third trimester [10,13,19].

We are conducting a prospective randomized clinical trial that will try to evaluate if a 35^{th}-37^{th} weeks ultrasound in low risk pregnancies is effective in reducing cesarean deliveries for intrapartum fetal distress and admissions to NICU. In parallel with this trial we consider that this observational study would reflect the experience of physicians and could contribute to update the guidelines of surveillance of low risk pregnancy.

The main limitation of our study was the low response rate, particularly the low response rate for GPs compared to GOs, probably because the first are less motivated with this subject since GOs deal more directly with the consequences of missing FGR. Despite the low response rate of GPs, we decided to analyse the data and stopped attempts to include more GPs since we identified important differences among the physicians included.

We may have lost some participants that may have changed e-mail without updating personal information at the registries of scientific societies. A selection bias could be associated with recruitment of physicians that have e-mail as well as physicians that attend scientific meetings that may be more motivated to be updated. Implementation of two modalities of recruitment may have minimized these biases.

Although we did not ask practitioners whether they are aware of guidelines for third trimester FGR screening in low risk pregnancies, practice and knowledge variation is apparent and suggests that providers may have controversial ideas about the screening of FGR. These instances indicate the need for further research, both to gain a better understanding of FGR optimal screening and to improve outcomes and optimize guidelines.

Acknowledgements

The authors would like to thank Dr John Groarke and Dr Alexandre Valentim-Lourenço, mentors of the program Portugal Clinical Scholars Research Training of Harvard Medical School for the careful revision and correction of the text.

This work was supported by a Research Grant from Fundação para a Ciência e Tecnologia (FCT) - SFRH/SINTD/92997/2013. The sponsor had no participation in the collection, analysis and interpretation of the data and in the writing of the manuscript.

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