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68

Ana María de la Peña Dieste Pérez

Predicción de las alteraciones de crecimiento fetal y efectos perinatales adversos por la ecografía del tercer trimestre

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PREDICCIÓN DE LAS ALTERACIONES DE CRECIMIENTO FETAL Y EFECTOS PERINATALES ADVERSOS POR LA ECOGRAFÍA DEL TERCER TRIMESTRE

Autor

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“Predicción de las alteraciones de crecimiento fetal y efectos adversos perinatales por la ecografía del tercer trimestre”

Memoria presentada por

PEÑA DIESTE PÉREZ

Para optar al grado de Doctor en Medicina y Cirugía por la Universidad de Zaragoza

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DECLARACIÓN DE TESIS POR COMPENDIO DE PUBLICACIONES

La Licenciada en Medicina y Facultativo Especialista de Área de Ginecología y Obstetricia Peña Dieste Pérez, solicita la presentación de su tesis doctoral por compendio de publicaciones en la Universidad de Zaragoza, con la unidad temática "Predicción de las alteraciones de crecimiento fetal y efectos perinatales adversos por la ecografía del tercer trimestre". Para ello hace constar las referencias de los artículos que componen dicha tesis:

1. Savirón-Cornudella R, Esteban L, M, Tajada-Duaso M, Castán-Mateo S, Dieste-Pérez P, Cotaina-Gracia L, Lerma-Puertas D, Sanz G, Pérez-López F, R: Detection of Adverse Perinatal Outcomes at Term Delivery Using Ultrasound Estimated Percentile Weight at 35 Weeks of Gestation: Comparison of Five Fetal Growth Standards. Fetal Diagn Ther 2020;47:104-114. doi: 10.1159/000500453.

2. Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, Dieste Pérez P, Pérez-López FR, Castán-Larraz B, Sanz G, Tajada-Duaso M. Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards. Fetal Diagn Ther. 2021;48(1):15-23. doi: 10.1159/000510020.

3. Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, Dieste-Pérez P, Pérez-López FR, Campillos JM, Castán-Larraz B, Sanz G, Tajada-Duaso M. Prediction of Late-Onset Small for Gestational Age and Fetal Growth Restriction by Fetal Biometry at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of Six Fetal Growth Standards. J Clin Med. 2021 Jul 3;10(13):2984. doi: 10.3390/jcm10132984.

4. Dieste Pérez P, Esteban LM, Savirón-Cornudella R, Pérez-López FR, Castán-Mateo S, Sanz G, Tajada-Duaso M. Reduced Growth in Non-Small for Gestational Age Fetuses from

35 Weeks of Gestation to Birth and Perinatal Outcomes. Fetal Diagn Ther. 2021;48(11-12):768-777. doi: 10.1159/000519639.

5. Dieste-Pérez, P.; Savirón-Cornudella, R.; Tajada-Duaso, M.; Pérez-López, F.R.; Castán-Mateo, S.; Sanz, G.; Esteban, L.M. Personalized Model to Predict Small for Gestational Age at Delivery Using Fetal Biometrics, Maternal Characteristics, and Pregnancy Biomarkers: A Retrospective Cohort Study of Births Assisted at a Spanish Hospital. *J. Pers. Med.* 2022, *12*, 762. https://doi.org/10.3390/jpm12050762.

MAURICIO TAJADA DUASO, Doctor en Medicina por la Universidad de Zaragoza

ACREDITA:

Que ANA MARÍA DE LA PEÑA DIESTE PÉREZ, graduada en Medicina, ha realizado bajo nuestra dirección el trabajo que les presenta como memoria para optar al grado de Doctor, con el título: "Predicción de las alteraciones de crecimiento fetal y efectos perinatales adversos por la ecografía del tercer trimestre". Después de su revisión, consideramos que reúne los requisitos exigidos por la Facultad de Medicina de la Universidad de Zaragoza para ser considerada como Tesis Doctoral por compendio de publicaciones, para ser defendida en sesión pública ante el tribunal que le sea asignado para juzgarla. Y para que conste, de acuerdo con la legislación vigente y a petición de la interesada, firma el presente certificado en Zaragoza, a 22 de diciembre de 2022.

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Que ANA MARIA DE LA PEÑA DIESTE PÉREZ, graduada en Medicina, ha realizado bajo nuestra dirección el trabajo que les presenta como memoria para optar al grado de Doctor, con el título: "Predicción de las alteraciones de crecimiento fetal y efectos perinatales adversos por la ecografía del tercer trimestre". Después de su revisión, consideramos que reúne los requisitos exigidos por la Facultad de Medicina de la Universidad de Zaragoza para ser considerada como Tesis Doctoral por compendio de publicaciones, para ser defendida en sesión pública ante el tribunal que le sea asignado para juzgarla. Y para que conste, de acuerdo con la legislación vigente y a petición de la interesada, firma el presente certificado en Zaragoza, a 22 de diciembre de 2022.

SAVIRON CORNUDELLA RICARDO MARIANO - 25475750F

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Fdo. Dr. RICARDO SAVIRON CORNUDELLA

INDICE DE CONTENIDOS

1. INTRODUCCION

1.1. INTRODUCCIÓN A LA ECOGRAFÍA DEL TERCER TRIMESTRE

1.1.1. ¿Qué objetivos tiene la ecografía del tercer trimestre universal-rutinaria?

No existen recomendaciones concretas en la mayoría de las sociedades científicas respecto a la práctica de una ecografía rutinaria en el tercer trimestre y tampoco hay consenso en cuanto a su contenido. Algunas sociedades científicas no recomiendan realizar esta ecografía a toda la población, basándose en los resultados de un metaanálisis publicado por la Cochrane en 2015[1] en el que no se encontró beneficio sobre el resultado perinatal.

La guía del Reino Unido de 2013[2] así como el National Health Service[3] o el National Institute for Health and Care Excellence[4] no hacen ninguna referencia sobre la utilidad de realizar una ecografía en el tercer trimestre en gestaciones de bajo riesgo. Tanto la guía de Estados Unidos de 2013[5] como el American College of Obstetricians and Gynecologists (ACOG)[6] en sus boletines periódicos y el American Institute of Ultrasound in Medicine[7] describen la clasificación, contenido e indicaciones de las exploraciones ecográficas del primer trimestre por un lado y por otro, de manera conjunta, para el segundo y tercer trimestre, sin diferenciar su contenido ni explicitar que deba realizarse la de tercer trimestre. En la guía del Royal Australian[8] and New Zealand College of Obstetricians and Gynaecologists de 2015 y su actualización de 2018 no se encuentran referencias claras a la ecografía del tercer trimestre ni tampoco en la de la Society of Obstetricians and Gynaecologists of Canada de 2017[9].

La International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) ha publicado guías de práctica clínica para la realización de la ecografía de primer y segundo trimestre[10,11], pero no para la de tercer trimestre. En la reciente guía de Evaluación ecográfica de la biometría y el crecimiento fetal publicada en 2019[12] consideran que el diagnóstico de las alteraciones del crecimiento y su manejo específico resulta útil, sin embargo determinan que cualquier exploración en el tercer trimestre dependerá de la práctica local, de la presencia o ausencia de patología materna o fetal, de factores de riesgo o hallazgos que puedan estar asociados con un crecimiento anormal y de las pautas institucionales, sin concederle, por tanto, el rango de recomendación sistemática para todas las gestantes y tampoco la ISUOG hace referencia a que esta ecografía del tercer

trimestre tenga otros objetivos diferentes a la evaluación del crecimiento fetal. La Organización Mundial de la Salud (OMS) no recomienda realizar ninguna ecografía de rutina después de la semana 24 de gestación. Únicamente acepta su realización si ésta no se hubiera hecho y con los únicos objetivos de identificar el número de fetos, la presentación fetal y la localización de la placenta[13].

Sin embargo cada vez son más los estudios que apoyan que la realización de una ecografía en el tercer trimestre de gestación en población de bajo riesgo, sí que parece mejorar el resultado perinatal[14–16] y que las estrategias actuales para monitorear el crecimiento fetal en el tercer trimestre como es la medición de la altura de fondo uterino no son suficientes para detectar la mayoría de las alteraciones de crecimiento fetal[17]. Ya son muchos países los que realizan de forma rutinaria esta exploración[18,19].

La Sociedad Española de Ginecología y Obstetricia (SEGO) en su última Guía de Asistencia Práctica de la Sección de Ecografía Obstétrico-Ginecológica, publicada en octubre de 2020 toma como objetivo justificar la realización de esta exploración a la vista del conocimiento actual. Define como ecografía del tercer trimestre de la gestación aquella exploración realizada entre la 32 y 36 semanas de gestación y cuyos objetivos son[20]:

- identificar la vitalidad y estática fetal
- diagnosticar las anomalías en la inserción placentaria
- diagnosticar las anomalías del volumen de líquido amniótico
- detectar las anomalías de la morfología fetal de expresión tardía
- evaluar el crecimiento fetal con el fin de diagnosticar alteraciones en el mismo

Es en el último objetivo mencionado, en torno al cual se desarrolla esta tesis.

La indicación y objetivo de la ecografía en el tercer trimestre de la gestación estará estrictamente ligado al tipo de embarazo, por tanto en aquellas gestaciones de riesgo, tanto el número, frecuencia y objetivo de la misma estará determinado por la patología subyacente.

1.1.2. ¿En qué momento hay que realizarla?

La recomendación de realizar una ecografía de cribado en el tercer trimestre se recoge desde hace años en las diferentes Guías de Asistencia Práctica de control gestacional de la SEGO[21]. Sin embargo, la edad gestacional en la que realizarla es motivo de discusión.

Según la Guía de Control Prenatal de la SEGO[21] y la Guía de la Exploración Ecográfica del tercer trimestre actualizada en el año 2020[20] debe realizarse entre las 34 y 36+6 semanas. No obstante, no todas las guías internacionales están de acuerdo.

Un estudio de Di Lorenzo et al de 1.868 embarazos informó que el peso fetal estimado (PFE) a las 30-32 semanas predijo el 73% de los recién nacidos pequeños para la edad gestacional (PEG) con peso al nacer por debajo del percentil 10, con una tasa de falsos positivos (TFP) del 25%[22]. Otro estudio de Souka et al de 2310 embarazos informó que PFE calculado a las 30-33 semanas de gestación predijo el 60 % de los recién nacidos PEG con peso al nacer por debajo del percentil 5, con una TFP del 10%[18] y los mismos autores estudiaron la capacidad predictiva del PFE en 2288 embarazos a las 34-37 semanas de gestación dando como resultado una tasa de detección del 75 % de los recién nacidos PEG con peso al nacer menos del percentil 5, con una TFP del 10 %, lo que fue superior a los resultados previos[23].

En el estudio de Fadigas et al.[24] al realizar un cribado combinado por características, historial materno y PFE a las 35-37 semanas, se predijo, con una TFP del 10 %, alrededor del 70 % de los embarazos que posteriormente dieron a luz un recién nacido PEG a término con un percentil menor del 5; lo que fue superior a la tasa de detección del 58 % lograda mediante el cribado a las 30-34 semanas del estudio de Bakalis[25]. Sin embargo en este mismo estudio de Bakalis et al. se informó que el cribado a las 32 semanas de gestación puede identificar, con una TFP del 10 %, alrededor del 90 % de los PEG con percentil menor de 5 con parto prematuro[25]. Por lo que hay que tener en cuenta que aunque una ecografía en el tercer trimestre a las 36 semanas, en lugar de a las 32 semanas, mejoraría la predicción de PEG con percentil menor de 5 y parto por encima de las 37 semanas del 58 % al 70 %, esto sería a expensas de perder fetos PEG con parto pretérmino[24].

En el estudio de Roma et al.[16] se determinó que el examen ecográfico realizado a las 36 semanas de gestación es más efectivo que el realizado a las 32 semanas para la detección tanto de fetos con crecimiento intrauterino restringido (CIR) como de resultados perinatales y neonatales adversos relacionados.

También en el año 2019 en un trabajo del grupo de Nicolaides se observa que cuanto menor es el intervalo entre la ecografía y el parto, mayor tasa de detección de anomalías en el crecimiento fetal se obtiene[26].

1.1.3. ¿Es necesario realizar la ecografía del tercer trimestre de manera universal o rutinaria?

La conveniencia de realizar una ecografía sistemática en el tercer trimestre a todas las gestantes, incluidas las de bajo riesgo, es objeto de controversia. Las recomendaciones de 14 países europeos, recogidas en el registro de Eurocat[27], indican que se realiza una ecografía rutinaria en el tercer trimestre en 6 países: Francia, Italia, España, Austria, Bélgica y Croacia, mientras que en 8 no se recomienda: Reino Unido, Irlanda, Países Bajos, Suiza, Suecia, Dinamarca, Finlandia y Malta salvo pacientes seleccionadas como de alto riesgo.

La guía de la Royal College of Obstetricians and Gynaecologists de 2014 (RCOG)[2], el ACOG en su último boletín de 2016[6] y la OMS[13] en su guía del mismo año no la recomiendan y la ISUOG en su última guía de 2019[12] no lo aclara.

Su práctica en nuestro país está consolidada. Su recomendación se recoge desde hace años en las distintas Guías de Asistencia Práctica de control gestacional[20,21]y en prácticamente el 100% de los hospitales se lleva a cabo[28].

1.2. ALTERACIONES DEL CRECIMIENTO FETAL

1.2.1. ¿Cómo calculamos el peso y el percentil del peso fetal por ecografía y qué fórmula y modelo de crecimiento es mejor utilizar para el cálculo de los mismos?

El crecimiento fetal depende de varios factores, entre ellos la función útero-placentaria, las enfermedades maternas, la función cardiovascular o las enfermedades cardíacas de la madre[12], la nutrición materna, la altitud, el tabaquismo y el uso de drogas ilícitas y la presencia de condiciones patológicas como infecciones, aneuploidías y algunas condiciones genéticas[29].

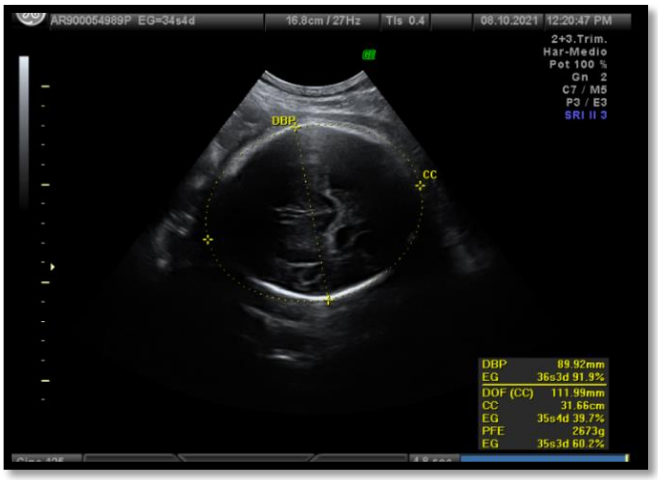
Sin embargo, la insuficiencia o disfunción útero-placentaria representa una de las causas más frecuentes de crecimiento anormal en un feto que por lo demás es normal[29].

En muchos países, la medición de la altura de fondo uterino en las gestantes es la principal herramienta de detección de alteraciones en el crecimiento en embarazos de bajo riesgo y la medición ecográfica de la biometría fetal se realiza únicamente cuando existen factores de riesgo o cuando la altura de fondo uterino es anormal[30–34]. Sin embargo, este planteamiento no logra identificar la mayoría de los recién nacidos con alteraciones en el crecimiento[35]. Un enfoque alternativo es realizar por lo tanto, una ecografía en el tercer trimestre para la estimación del peso fetal.

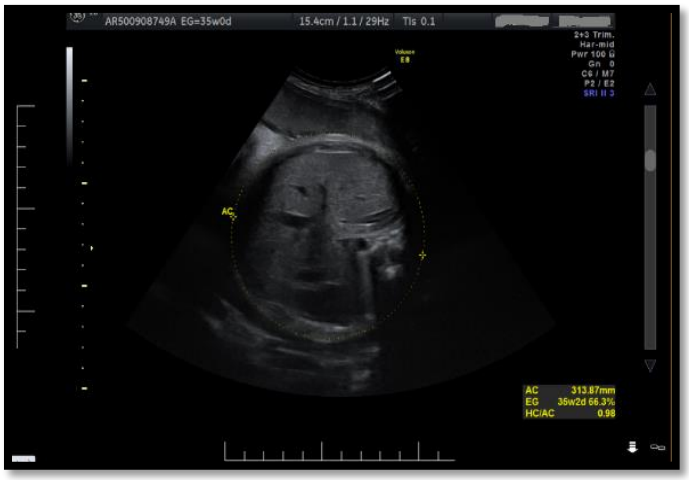
Peso fetal estimado

El tamaño del feto se determina mediante la evaluación biométrica de la circunferencia cefálica (CC), el diámetro biparietal (DBP), la circunferencia abdominal (CA) y la longitud del fémur (LF) determinando con esas medidas un PFE, el cual puede ser calculado mediante diferentes fórmulas[11,29]. Estas medidas se adquieren en cortes estandarizados siguiendo unos criterios estrictos de calidad[11,36] (Figura 1):

A



B



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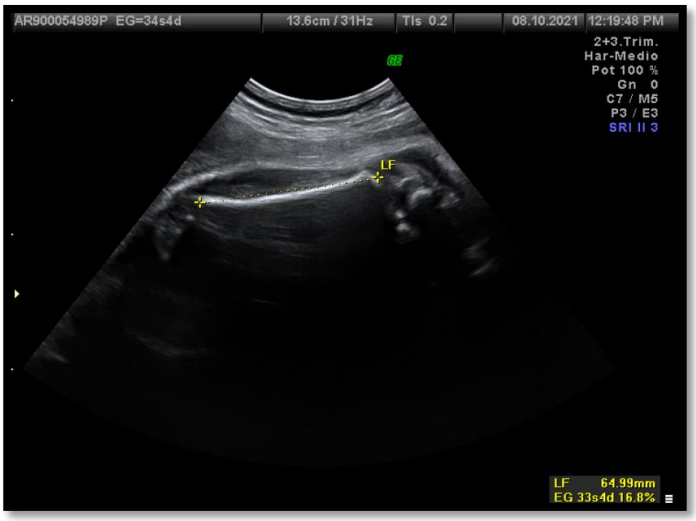

Figura 1. A) Biometría de diámetro biparietal y circunferencia cefálica. B) Biometría de circunferencia abdominal. C) Biometría de longitud de fémur.

Una vez realizadas estas biometrías, se estima el peso fetal mediante distintas fórmulas matemáticas (Figura 2 y 3). Hoy en día las más extendidas son, las fórmulas de Hadlock et al.[37] que utiliza el DBP, CC, CA y LF y la fórmula de Stirnemann et al.[38] que incluye las medidas de CC y CA únicamente. Todas las fórmulas emplean dos o más parámetros

somatométricos para realizar una estimación más o menos aproximada del peso fetal. Los resultados pierden precisión según se incrementa el peso fetal[39].

Figura 2. Fórmula de Hadlock (1985)[37]

New regression models based on an expanded sample population (n = 276 fetuses)

Fetal parameters	*Regression equations**
Abdominal circumference, femur length	Log_{10} weight = 1.304 + 0.05281 AC + 0.1938 FL − 0.004 AC × FL
Biparietal diameter, abdominal circumference, femur length	Log_{10} weight = 1.335 − 0.0034 AC × FL + 0.0316 BPD + 0.0457 AC + 0.1623 FL
Head circumference, abdominal circumference, femur length	Log_{10} weight = 1.326 − 0.00326 AC × FL + 0.0107 HC + 0.0438 AC + 0.158 FL
Biparietal diameter, head circumference, abdominal circumference, femur length	Log_{10} weight = 1.3596 − 0.00386 AC × FL + 0.0064 HC + 0.00061 BPD × AC + 0.0424 AC + 0.174 FL

*AC, abdominal circumference; FL, femur length; BPD, biparietal diameter; HC, head circumference.

Figura 3. Fórmula de Stirnemann-INTERGROWTH-21st (2017)[38]

$$\text{Log (PFE)} = 5.084820 - 54.06633 \times (CA/100)3 - 95.80076 \times (CA/100)3 \times \log (CA/100) + 3.136370 \times (CC/100)$$

* PFE: peso fetal estimado; CA: circunferencia abdominal; CC: circunferencia cefálica

Varios estudios han comparado la precisión de varias de estas ecuaciones. La mayoría concluye que las ecuaciones basadas en 3 o 4 índices biométricos (en lugar de solo 1 o 2 índices) obtienen resultados más consistentes y precisos. Una revisión sistemática reciente[40] encontró que la ecuación de Hadlock, basada en tres índices (CC, CA y LF: peso Log10 = 1,326 − 0,00326*CA*LF + 0,0107*CC + 0,0438*CA + 0,158*LF)[37], proporciona la mayor precisión. Dado que la precisión de las diversas ecuaciones puede variar entre diferentes poblaciones, puede ser razonable que los radiólogos, ecografistas u obstetras elijan una ecuación que haya sido validada dentro de su población local y dentro del rango de edad gestacional en el que se utiliza[41].

El PFE puede ser utilizado para controlar el tamaño y el crecimiento fetal[42]. Su uso también tiene desventajas[43,44], los errores en las mediciones de un solo parámetro se multiplican; existen variabilidad intra e interobservador, encontrando errores

habituales[45] en el rango del 10-15%; y precisamente estos errores son relativamente mayores en los fetos en los que existe un mayor interés diagnóstico, es decir, aquellos que son PEG o grandes para la edad gestacional (GEG) y además se ve afectado por factores como el sexo fetal, la presentación y la pluralidad (mayor en gestaciones gemelares)[46–53].

Fenotipos fetales muy diferentes pueden tener el mismo PFE, por ejemplo, un feto con CC grande y CA pequeña puede tener el mismo PFE que un feto con CC pequeña y CA grande[42].

Percentil de peso estimado (PPE):

Las mediciones realizadas en una exploración ecográfica fetal pueden ser informadas como dato bruto, expresados en mm o en cm[54] o en formato de percentiles, Z-score, porcentaje de desviación de la mediana y múltiplos de la mediana[55] al relacionar dicho dato bruto con su rango de referencia.

El uso de Z-scores tiene la ventaja de que permite la comparación entre distintas variables biométricas en diferentes edades gestacionales[56], sin embargo los percentiles son intuitivamente más comprensibles. Existe una relación precisa entre ambos cuando la distribución de la población es normal (el percentil 5 equivale a 1.64 del Z-score; el percentil 10 equivale a 1.28 del Z-score)[57].

Una vez calculado el PFE y su correspondiente PPE, éste debe compararse con alguno de los nomogramas específicos dedicados para este fin. Los estándares de crecimiento poblacionales informan sobre cómo una población "debería crecer"[42].

Se ha demostrado que la elección del modelo de crecimiento tiene un impacto considerable en la proporción de fetos clasificados como PEG o GEG[58,59].

Modelos de crecimiento poblacionales

Los estándares o modelos de crecimiento son tablas prescriptivas que se basan únicamente en embarazos de bajo riesgo o sin complicaciones, y como tales brindan

información sobre cuál es el crecimiento fetal óptimo. Existe variación entre los diferentes modelos de crecimiento con respecto a la definición de embarazos de "bajo riesgo"; mientras que algunos excluyen a las mujeres con condiciones médicas preexistentes y complicaciones del embarazo, otros también excluyen a las mujeres por debajo o por encima de cierta altura o peso, mujeres con nutrición subóptima, nivel socioeconómico bajo, exposición a la contaminación del aire, gran altitud, etc[41].

En la actualidad, el diagnóstico prenatal del crecimiento fetal anormal se basa en la discrepancia entre el PFE por ecografía para un feto determinado y el esperado para las semanas de gestación de acuerdo con una de esos modelos de crecimiento [43,60], teniendo en cuenta los percentiles 10 y 90 como limites por debajo y por encima respectivamente, para identificar a los fetos en riesgo de desenlace perinatal adverso[61].

Existen múltiples modelos para evaluar el crecimiento fetal (Tabla 1). Casi todos se derivan de estudios con gran heterogeneidad metodológica[62], lo que ha derivado en una amplia variación en los límites de los valores reportados que dificulta su interpretación clínica. La elección entre las diferentes referencias, o estándares para la evaluación del crecimiento fetal, afecta al porcentaje de fetos en riesgo de desenlace perinatal adverso.

Dentro de estos modelos poblacionales encontramos, por un lado, los modelos universales que se basan en el supuesto de que, en condiciones óptimas, se espera que todos los fetos tengan el mismo potencial de crecimiento, independientemente de su país de origen o raza, y que la única razón de las diferencias observados se deben a factores ambientales, como la desnutrición y las toxinas ambientales. Estos modelos basados en ecografías se desarrollan a través de estudios longitudinales prospectivos multicéntricos y multinacionales, en los que los datos sobre el crecimiento fetal ecográfico de varios países se agrupan en un único gráfico universal internacional[41]. Los mejores ejemplos de tales modelos universales son los del Proyecto INTERGROWTH-21st[38,42,63] y el de la OMS[64]. Son las referencias que la ISUOG considera de elección y que adicionalmente tienen la ventaja de permitir el seguimiento y evaluación del crecimiento en vida posnatal[54]. Ambos estudios incluyen población de diferentes países y continentes: 11 países en INTERGROWTH- 21st Project (Brasil, China, Inglaterra, India, Italia, Kenia, Omán, Pakistán, Sudáfrica, Tailandia y Estados Unidos) y 10 países en el de la OMS (Argentina, Brasil, República Democrática del Congo, Dinamarca, Egipto, Francia,

Alemania, India, Noruega y Tailandia). El estándar INTERGROWTH-21st propuso el uso de la fórmula de Stirnemann et al.[38] para estimar el peso fetal en lugar de la clásica y más utilizada de Hadlock et al[37].

El grupo de Nicolaides crea sus propias tablas de pesos fetales locales de la Fetal Medicine Foundation (FMF) no personalizadas y hace una comparación entre éstas y las comentadas anteriormente, concluyendo que no es correcto incluir diferentes grupos raciales y cuestiona ajustar o personalizar las tablas con las variables de peso materno, altura y paridad. Aporta como ejemplo que, para la 36 semana de gestación, su percentil 10 sería de 2531 gramos, en tanto que para la OMS e INTERGROWTH se situaría en 2352 gramos y 2144 gramos respectivamente[65].

Por otro lado, también se han propuesto modelos personalizados y condicionales como alternativa[66,67]**.** Los modelos de referencia personalizados son utilizados para ajustar variables conocidas que afectan al peso y crecimiento fetal, tales como la altura y peso materno, origen étnico, paridad y sexo fetal. Un modelo personalizado clasificará una diferente proporción de fetos como PEG al momento del nacimiento, comparada con los modelos de referencia no personalizados. Esto puede ser relevante para las unidades en las cuales la población prenatal es diversa respecto a aquellos factores, dado que podrán detectar mejor a los fetos que se encuentran en riesgo de complicaciones perinatales, aunque dicho beneficio de los modelos personalizados no ha sido demostrado[15].

Ejemplos de dichos modelos son los del Instituto Nacional de Salud Infantil y Desarrollo Humano que son específicos de raza diferenciando entre mujeres blancas, negras, hispanas y asiáticas[66] o el estándar personalizado de la Rama de Investigación de Perinatología/Instituto Nacional de Salud Infantil y Desarrollo Humano Eunice Kennedy Shriver publicado para mujeres afroamericanas[68]. El software Gestation Related Optimal Weight personaliza su tabla para otros factores fisiológicos como la altura, el peso, la paridad de la madre y el sexo fetal[67,69].

En nuestro medio, el modelo de Figueras et al.[70], local y personalizado de amplia difusión, es el recomendado en el documento de consenso de la SEGO[71]. Según la calculadora de Figueras et al. el percentil 10 para la 36 semana es de 2320 gramos para feto masculino y 2250 gramos para femenino.

El RCOG[2] recomienda el uso de curvas de peso al nacer personalizadas para identificar fetos PEG; apoya que el ajuste del peso fetal debe realizarse de forma individual y no por población.

En esta tendencia de crear modelos nacionales o de grupos poblacionales más limitados, el Hospital Universitario Miguel Servet (HUMS) creó sus propias tablas de crecimiento. Una personalizada para paridad, edad, índice de masa corporal y altura materna, altura paterna y sexo fetal utilizando la fórmula de Hadlock [37] ajustado a nuestra población con un coeficiente de variación que cambia con la edad gestacional y otra no personalizada[72].

La utilización de modelos personalizados sigue siendo un aspecto controvertido, en tanto que para algunos grupos suponen mejores resultados[66,70,73,74] otros cuestionan estos beneficios[10] y tampoco las diferentes sociedades científicas han llegado a acordar una posición unánime.

Trasladando a los diferentes modelos de referencia simulaciones de peso en diversa edad gestacional, el percentil obtenido puede oscilar hasta entre el percentil 3 y el 25. Estas diferencias tienen su trascendencia clínica, pues además de que se incluirían como PEG-CIR a algunos fetos que no lo son, se podría excluir de controles a los verdaderamente CIR, lo que quizás tendría impacto pronóstico, pues, al no identificarse algunos fetos de riesgo, podrían terminar en muerte intrauterina o llegar al inicio de parto espontáneo en condiciones de hipoxia o acidosis. Por el contrario, si por error se incluyen fetos de bajo riesgo, se está exponiendo tanto a la madre como al feto a una sobrevigilancia que podría ocasionar un intervencionismo no justificado[28].

Tabla 1. Comparativa de estándares poblacionales.

	OMS (Kiseraud 2017)[64]	INTERGROWTH-21st (Stirnemann 2014)[42]	FMF (Nicolaides 2018)[65]	GROW (Gardosi 1992)[67]	Hospital Clinic Barcelona (Figueras 2008)[70]	HUMS (Saviron-Cornudella 2018)[72]
Localización	Internacional (10 países)	Internacional (11 países)	Local (Londres)	Nacional (Inglaterra)	Local (Barcelona)	Local (Zaragoza)
Población	Distintas poblaciones	Distintas poblaciones	Local (influyen etnias)	Nacional	Local	Local
Ajuste	No (Sexo fetal)	No (Sexo fetal)	No (Sexo fetal)	Si	Si	2 modelos (ajustado/ sin ajustar)
Fórmula cálculo peso fetal estimado	Hadlock	Stirnemann	Hadlock	Hadlock	Hadlock	Hadlock

*GROW: Gestation Related Optimal Weight

En los últimos años ha habido un debate continuo sobre el modelo de crecimiento óptimo que se debe usar, y numerosos estudios han comparado el rendimiento de una amplia variedad de modelos en diferentes poblaciones con resultados contradictorios[41].

En el último consenso de la Federación Internacional de Ginecología y Obstetricia de 2021[41] proponen que los modelos universales como el de INTERGROWTH-21st[42], en el que los datos proporcionados se basan en una estimación del crecimiento fisiológico o normal en condiciones ideales, serán similares en diferentes poblaciones en condiciones óptimas y que por lo tanto pueden usarse universalmente, eliminando la necesidad de estándares locales.

Sin embargo, es probable que los modelos universales identifiquen más fetos con un peso por debajo del percentil 10 en poblaciones donde haya muchos factores desfavorables, como la desnutrición o la hipertensión que puedan afectar negativamente el crecimiento fetal[41]. Ésta puede ser una de las razones por las que por ejemplo en la India el 50% de

los recién nacidos tienen un peso al nacer por debajo del percentil 10 según el modelo INTERGROWTH-21st[75].

Según la Federación Internacional de Ginecología y Obstetricia en su iniciativa sobre el crecimiento fetal en la que aporta consejos de mejores prácticas para la detección, el diagnóstico y el tratamiento de la restricción del crecimiento fetal, la decisión sobre qué modelo utilizar se debería basar en una comparación del rendimiento de las diversas opciones que existen en la población de interés. Esto se puede lograr mediante los siguientes enfoques[41]:

1. validación estadística: encontrar la tabla que mejor se corresponda con la distribución del peso fetal en embarazos de bajo riesgo en la población local. Es decir, identificar la tabla que, cuando se aplica a la población local, arroja percentiles de peso que siguen una distribución normal centrada aproximadamente en el percentil 50 y que identifica aproximadamente al 10% de la población de bajo riesgo por debajo del percentil 10 y por encima del percentil 90, y aproximadamente el 5% de la población por debajo del percentil 5 y por encima del percentil 95.

2. validación basada en resultados: encontrar el modelo para el cual el diagnóstico de PEG tiene el mejor valor predictivo para resultados adversos relacionados con retraso del crecimiento[76,77] pero con TFP correcta.

Encontrar el modelo que proporcione el mejor equilibrio entre estos dos enfoques requiere una cuidadosa consideración y debe basarse en una definición clara de los objetivos de la detección[41].

1.2.2. ¿Qué se considera una anomalía del crecimiento fetal y qué implicaciones perinatales tienen las anomalías del crecimiento?

Los desórdenes que podemos encontrar con respecto al crecimiento fetal consisten principalmente en dos situaciones: por un lado, las anomalías por defecto, en las que encontramos la restricción del crecimiento fetal o CIR, relacionado con el feto PEG; y, por otro lado, las anomalías por exceso, el denominado feto GEG, el cual puede convertirse en macrosomía fetal[54].

Crecimiento intrauterino restringido versus pequeño para la edad gestacional.

La restricción del crecimiento fetal se define como la imposibilidad de alcanzar el potencial de crecimiento predefinido[78]. La evidencia clínica sugiere que existen, al menos, dos grupos de fetos pequeños, los denominados fetos CIR y PEG[78].

CIR se usa normalmente para referirse a fetos pequeños con mayor riesgo de deterioro fetal en el útero, mortinatos y resultados perinatales más pobres en general en comparación con los fetos de crecimiento normal, debido a un factor patológico, más comúnmente disfunción placentaria[41]. Se cree que estos fetos tienen una restricción de crecimiento "verdadera". En general, un feto CIR se asocia con signos de velocimetría Doppler que sugieren una redistribución hemodinámica como reflejo de la adaptación fetal a la desnutrición o hipoxia, signos histológicos y bioquímicos de enfermedad placentaria y un mayor riesgo de preeclampsia[78]**.** Estos fetos tienen un riesgo 5 a 10 veces mayor de muerte intrauterina y un mayor riesgo de morbilidad y mortalidad perinatal y resultados subóptimos a largo plazo[79–82].

El término PEG se ha utilizado para diferenciar un subgrupo de fetos pequeños cuyo PFE está por debajo de un punto de corte determinado[83,84], que no presentan los cambios descritos anteriormente, por lo que parece no haber adaptación fetal a un ambiente anormal y con resultados perinatales similares a los fetos de crecimiento normal[78].

Aunque ambas definiciones parezcan claras, en la práctica clínica, la diferenciación entre ambos grupos no es sencilla y las guías de práctica clínica tanto nacionales como internacionales no se ponen de acuerdo con los criterios de definición, existiendo controversia en varios aspectos.

Según la ACOG[31] en su boletín de 2019, el término CIR se utiliza para describir fetos con un PFE inferior al percentil 10 para la edad gestacional, mientras que el término PEG se utilizará exclusivamente para describir a los recién nacidos cuyo peso al nacer es menor del percentil 10 para la edad gestacional.

De acuerdo con la Federación Internacional de Ginecología y Obstetricia[41] en su última guía publicada en 2021, PEG se define como un PFE o un peso al nacer por debajo del percentil 10 para la edad gestacional. Mientras que la definición de CIR recomiendan que

se base en una combinación de medidas del percentil de tamaño fetal y alteraciones en la velocimetría Doppler de la circulación feto-placentaria. Sin embargo, también exponen que, en entornos de bajos recursos, el CIR se puede definir de la misma manera que PEG, o sea un PFE o peso al nacer por debajo del percentil 10 para la edad gestacional.

En la guía de práctica clínica de la ISUOG[29] sobre el diagnóstico y manejo del feto PEG y restricción del crecimiento fetal de 2020, apoyan los términos definidos en el consenso internacional de Delphi[85], en los que se propuso que un punto de corte de CA o PFE por debajo del percentil 3 puede usarse como el único criterio de diagnóstico para CIR y en caso de CA o PFE por debajo del percentil 10, el diagnóstico de CIR debe considerarse solo en asociación con otros parámetros.

En la última guía publicada por la RCOG[2] del año 2013 definen un feto PEG aquel con un PFE o una CA inferior al percentil 10 y PEG grave como un PFE o CA inferior al percentil 3.

Con respecto a las guías nacionales, el protocolo del Hospital Clinic de Barcelona llevado a cabo por Figueras y Gratacós en 2014[78], actualizado en 2019[86] y la Guía de Asistencia práctica de la SEGO[20] del año 2020 definen como feto PEG aquel que tiene un PFE entre 3 y 10 para la edad gestacional con estudio de velocimetría Doppler dentro de la normalidad, mientras que un feto CIR lo definen como aquel con un PFE inferior al percentil 3 o un PFE inferior al percentil 10 pero con alteración del flujo cerebro-umbilical o de las arterias uterinas[78].

Como he expuesto, considerar un punto de corte por debajo del percentil 10 para la CA y / o PFE es una definición comúnmente aceptada de restricción de crecimiento. Sin embargo, el valor de corte del décimo percentil para cada edad gestacional varía dependiendo del modelo de crecimiento poblacional utilizado. Cuanto más bajo es el límite inferior normal fijado para la CA y el PFE, mayor es la correlación entre fetos y riesgo por verdadera restricción de crecimiento fetal[15]. Por ello el Consenso Internacional desarrollado con metodología Delphi propuso que un punto de corte de CA o PFE por debajo del percentil 3 puede utilizarse como único criterio de diagnóstico para CIR[85].

Para diferenciar entre PEG y CIR en los casos en los que el tamaño del feto está entre un percentil 3 y 10, se requieren por lo tanto parámetros biofísicos adicionales. El más conocido es la evaluación de la velocimetría Doppler en las circulaciones placentaria y

fetal, pero se estudian otros como la evaluación de la velocidad de crecimiento del feto, el uso de gráficos de crecimiento personalizados, y el uso de biomarcadores[29].

A su vez, los fetos CIR se han clasificado según la edad gestacional en el momento del diagnóstico, en CIR de inicio temprano (menor de 32 semanas) y CIR de inicio tardío (mayor o igual a 32 semanas). El fundamento de esta clasificación se basa en las diferencias entre estos dos fenotipos de CIR en cuanto a gravedad, evolución natural, hallazgos en el estudio de velocimetría Doppler, asociación con complicaciones hipertensivas, hallazgos placentarios y manejo tras su diagnóstico[29,78,85,87–89]. Son las de comienzo tardío los que suponen un reto diagnóstico durante el tercer trimestre de gestación (Tabla 2).

Tabla 2: Definiciones basadas en el consenso para la restricción del crecimiento fetal temprana y tardía en ausencia de anomalías congénitas[85]

CIR precoz	CIR tardío
EG <32 semanas sin anomalias congénitas	EG >32 semanas sin anomalias congénitas
CA/PFE < p3 o FFDA-AU ó 1. CA/PFE <p10 combinado con: 2. IP AUt > p95 y/o 3. IP AU > p95	CA/PFE < p3 o al menos dos de tres de: 1. CA/PFE <p10 2. CA/PFE cruzando más de dos cuartiles * 3. RCP <p5 o IP AU > p95

*Percentiles de crecimiento no personalizados. CA: circunferencia abdominal. FFDA: flujo de fin de diástole ausente. RCP: relación cerebro-placentaria. PFE: peso fetal estimado. EG: edad gesatcional. IP: índice pulsatilidad. AU: arteria umbilical. AUt: arteria uterina.

Los CIR de inicio temprano tienen una prevalencia del 20-30%[29,90] con respecto al total de fetos CIR, suelen ser más graves y es más probable que se asocien con anomalías en el Doppler de la arteria umbilical. La patología placentaria subyacente es con frecuencia similar a la observada en los casos de preeclampsia de aparición temprana (perfusión vascular materna defectuosa), lo que explica la fuerte asociación con dicha patología.

Suelen ser más fáciles de detectar y la evolución natural tiende a seguir una secuencia predecible de cambios Doppler en la arteria umbilical y el conducto venoso[41]. El principal desafío de estos casos de inicio temprano es el manejo, es decir, el momento de finalización de la gestación, al intentar determinar el equilibrio óptimo entre los riesgos de muerte fetal intrauterina y prematuridad[90].

Los CIR de inicio tardío son más frecuentes, con una prevalencia del 70-80%[29,90]. A diferencia de los CIR precoces, por lo general son más leves, es menos probable que se asocien con preeclampsia y generalmente se asocian con un Doppler de la arteria umbilical normal. Por lo tanto, el principal desafío con estos fetos es el diagnóstico. El manejo, es decir, el momento de finalización de la gestación es relativamente simple dado que se suelen diagnosticar en etapas de pretérmino tardío o a ya en gestación a término, donde los riesgos asociados con el parto prematuro son menores. Dado que los estudios Doppler de la arteria umbilical y del conducto venoso suelen ser normales en los casos de CIR tardío, su diagnóstico se basa principalmente en la detección de los cambios adaptativos de la circulación cerebral, es decir una baja resistencia al flujo en la arteria cerebral media, lo que genera una relación del cociente cerebro-placentario baja. La evolución natural en estos casos es menos predecible, existiendo el riesgo de descompensación súbita y muerte fetal[78,90].

Clínicamente, la restricción de crecimiento se refleja en una caída en los percentiles de tamaño fetal a lo largo de la gestación. Sin embargo, el potencial de crecimiento fetal es difícil de determinar ya que, por lo general, no se dispone de evaluaciones seriadas del tamaño fetal para detectar una caída en el percentil de peso fetal. Es más, se suele tener una única estimación del peso fetal en un momento determinado a lo largo del tercer trimestre de la gestación. Por lo tanto, en la práctica clínica el diagnóstico de un feto PEG, es decir un feto con un percentil de peso por debajo de 10, se utiliza para sospechar restricción de crecimiento[41].

Sin embargo, el uso de PEG como sustitutivo de CIR tiene varias limitaciones. En primer lugar, la mayoría de los fetos PEG son fetos pequeños constitucionalmente sanos, cuyo menor tamaño es simplemente el resultado de su potencial de crecimiento predeterminado (es decir, un diagnóstico falso positivo de CIR). En segundo lugar, algunos

fetos con restricción de crecimiento, según su potencial de crecimiento original y el momento de la lesión, pueden permanecer por encima del percentil 10 y, por lo tanto, pueden no ser PEG en el momento de realizar la ecografía, pero tener un mayor riesgo de resultados adversos tanto perinatales como a largo plazo[15,91–94] (es decir, un diagnóstico falso negativo de CIR). En tercer lugar, el uso de PEG como sustituto de CIR está limitado por la precisión de la estimación ecográfica del peso fetal, que tiene un error de estimación de hasta 15%–20% y por el modelo de crecimiento poblacional que se utilice, lo que puede tener un efecto considerable en la proporción de fetos o recién nacidos señalados como PEG en una población determinada[41].

Desde un punto de vista clínico, la distinción entre CIR y PEG es relevante debido a la correlación con el resultado perinatal. Existe consenso entre la mayor parte de las guías en que se debe finalizar de manera electiva un feto CIR cuando se considera la maduración pulmonar, o antes si se observan signos de deterioro fetal[29,30,78]. Por el contrario, los fetos PEG se asocian con un resultado perinatal virtualmente normal y, en general, se considera que el manejo activo o la finalización electiva antes del término no ofrece ningún beneficio[78].

Las alteraciones del crecimiento fetal son prevalentes. Se estima que un 10% de fetos serán PEG, lo que significaría alrededor de 500.000 casos cada año en Europa[95]. Y hasta el 30% de los casos de mortalidad fetal se asocian a restricción de crecimiento o a fetos PEG a finales del tercer trimestre[96,97].

Una vez que se sospeche o se diagnostique un feto con alteración en el crecimiento, el embarazo debe ser monitorizado y manejado en unidades de medicina fetal y neonatal de nivel terciario[98]. Es importante el asesoramiento multidisciplinario de especialistas en neonatología y medicina materno-fetal.

Feto grande para la edad gestacional

La falta de consenso respecto a la macrosomía todavía es mayor que para el CIR, tanto en la definición como en las complicaciones, justificación de su cribado, manejo, etc.

Diferenciamos entre el término macrosoma, definido como aquel neonato con peso al nacer superior a los 4000 o 4500 gramos, en función de la guía, sea cual sea la edad gestacional[54,99–103]. Y feto GEG es aquel feto cuyo tamaño se encuentra por encima de un límite predeterminado para su edad gestacional. Los fetos GEG típicamente tienen el PFE o el CA por encima del percentil 90, aunque también se encuentran descritos en la literatura, otros puntos de corte como son el percentil 95, percentil 97, y la desviación de +2DE y +2 Z-score[12,54].

Si bien los problemas del feto grande han recibido menor atención que los del feto pequeño, se debe tener presente que la macrosomía fetal tiene un impacto importante sobre el pronóstico materno-fetal, que puede conllevar complicaciones médico-legales y la ecografía del tercer trimestre parece ser también la mejor herramienta disponible para su cribado[99,104,105].

Los principales riesgos maternos se centran en una mayor tasa de partos instrumentales, cesáreas, trauma perineal (incluyendo lesiones del esfínter anal), rotura uterina, hemorragia posparto y secuelas posteriores del suelo pélvico. En cuanto a los riesgos fetales, se encuentran aquellos que se producen intraparto y están relacionados con la distocia de hombros: lesiones del plexo braquial y fracturas óseas (clavícula, húmero), y otros como hipoglucemia, policitemia, hiperbilirrubinemia, asfixia perinatal, aumento de ingresos en la Unidad de Cuidados Intensivos (UCI) neonatal, encefalopatía hipóxico-isquémica y muerte perinatal[99,104,105].

La prevalencia teórica del macrosoma en países desarrollados oscila entre el 8 y 10%, aunque durante el seguimiento periódico de la gestación muchos de estos fetos GEG son identificados y, en consecuencia, la incidencia real del macrosoma es menor[99–101].

Un ensayo controlado aleatorizado publicado en 2015 mostró que la inducción del trabajo de parto puede disminuir la morbilidad perinatal en recién nacidos que pesan más de 4000 g o por encima del percentil 95[106], de ahí el interés clínico en la detección temprana de los fetos GEG.

Las tasas de detección de fetos por encima del percentil 90 en las mejores series se sitúan en torno al 50.9% con una TFP del 10%[107,108].

Ambas situaciones, tanto la restricción de crecimiento como el crecimiento excesivo, han sido relacionadas con resultados perinatales adversos (RPA), entendiendo como tal: puntuación de Apgar a los 5 minutos por debajo de 7, Ph de sangre arterial menor a 7.10, cesárea o parto instrumental por riesgo de pérdida de bienestar fetal, ingreso en UCI neonatal[30,109–111], y mayor riesgo de mortalidad perinatal[112–116]. Por lo que un diagnóstico correcto o precoz de los desórdenes de crecimiento deriva en una estrategia de prevención de estos RPA.

1.2.3. ¿Es recomendable realizar la ecografía del tercer trimestre de forma rutinaria-universal vs contingente-selectiva para la detección de alteraciones del crecimiento fetal?

Aunque la tendencia es recomendar su práctica sistemática, tampoco hay acuerdo sobre si la ecografía del tercer trimestre debe ser rutinaria o contingente en función de los riesgos calculados en el primer y segundo trimestre.

Según el estudio de EuroNatal de 2013[117], que analiza las diferencias en la mortalidad perinatal en diez regiones europeas, sugiere que la instauración de un adecuado programa de detección y manejo del CIR reduciría notablemente la mortalidad perinatal, ya que considera el no diagnóstico del CIR el factor de atención subóptima evitable más frecuente. Tanto Lindqvist en 2005[19] como Gardosi en 2013[113] estimaron que los fetos PEG diagnosticados antes del nacimiento que se someten a la vigilancia y parto electivo tienen una reducción de 4 a 5 veces en la mortalidad y/o morbilidad. El estudio ROUTE[16] también encuentra beneficios en la detección del CIR y Nohuz, en una serie de 24.946 gestantes con fetos nacidos por debajo del percentil 5, concluye que la identificación prenatal no pareció mejorar la morbilidad neonatal global, pero sí redujo la tasa de muerte fetal[97].

Sin embargo, tanto la RCOG[2], la ACOG[6] y la OMS[13] no recomiendan la realización de la ecografía del tercer trimestre de manera universal o rutinaria en el tercer trimestre. La mayoría de estos trabajos se basan en un metaanálisis de la Cochrane de 2015[1] donde concluyen que ecografía de rutina al final del embarazo en poblaciones de bajo riesgo o no seleccionadas no confiere beneficios ni para la madre ni para el recién nacido.

Desde 2015 han aparecido otros estudios que apoyan la realización de manera universal. Sovio et al. en 2015[15] concluye que la realización de la ecografía de manera universal multiplicaría por 3 la detección de fetos PEG con respecto a su realización de forma selectiva. Aumentaría la tasa de detección de 20% a 57% en casos de fetos PEG. Un estudio de Triunfo de 2016 demuestra que, si es rutinaria, se alcanzaría una tasa de detección de fetos PEG del 74% con una TFP del 10%, mientras que si se plantea un modelo contingente sería preciso hacer una ecografía al 50% de la población para obtener unos resultados similares[118].

En el caso de las anomalías por exceso, en un ensayo controlado aleatorizado publicado en 2015 mostró que la inducción del trabajo de parto puede disminuir la morbilidad perinatal en recién nacidos que pesan más de 4000 g o por encima del percentil 95[106] de ahí el interés clínico en la detección temprana de fetos GEG. Además, como se ha sugerido, el cribado GEG universal frente al selectivo en el tercer trimestre mejora la tasa de detección en el momento del parto[119].

En los últimos años se empieza a disponer de estudios que demuestran que, si únicamente se considera el cribado de los defectos de crecimiento fetal con la consiguiente puesta en marcha de los controles específicos y finalización de la gestación en el momento adecuado, ya se están obteniendo potenciales beneficios, pues, dependiendo de la severidad, el riesgo de mortalidad perinatal entre el grupo de fetos CIR puede aumentar hasta 5-10 veces[16]. Pero además, la ecografía del tercer trimestre puede utilizarse como hemos expuesto en sus objetivos, para diagnosticar una mala presentación fetal[120], trastornos del líquido amniótico y anomalías fetales[121,122] especialmente cuando se combina con mediciones de Doppler y biomarcadores químicos[123–126]. Sin embargo, no hay evidencia de que esta información mejore los resultados cuando se realiza de forma rutinaria en embarazos de bajo riesgo[41].

1.2.4. Nuevas estrategias para la predicción de las alteraciones en el crecimiento.

Existe evidencia de que la predicción de PEG mejora cuando, en primer lugar, se utiliza la biometría de rutina del tercer trimestre en lugar de la ecografía selectiva basada en factores de riesgo maternos y mediciones seriadas de la altura de fondo uterino[15], en

segundo lugar, se utiliza PFE en lugar de CA fetal[127,128] y, tercero, la exploración se realiza a las 36 semanas en lugar de a las 32 semanas de gestación[16,23,127]. Sin embargo, esto tiene tasas de detección bastante bajas, que van del 50 % al 80 %[129].

Por ello, se está estudiando la adición de otras estrategias como la utilización de la velocidad de crecimiento o la adicción de otros marcadores, como características maternas y parámetros bioquímicos y biofísicos para mejorar dichas tasas de detección.

Velocidad de crecimiento

Es importante diferenciar entre el concepto de tamaño fetal en un momento determinado, del concepto de crecimiento fetal, siendo este último un proceso dinámico, cuya valoración requiere al menos dos ecografías separadas en el tiempo[54].

La velocidad de crecimiento fetal se define como el cambio en el tamaño fetal entre 2 puntos temporales durante la gestación[130,131]. Este enfoque se puede aplicar al cambio en un índice biométrico fetal específico (por ej., CA o DBP) o al PFE, y generalmente se expresa como un cambio en el valor absoluto del índice biométrico por unidad de tiempo (por ej., mm/semana o g/día) o como un cambio en la puntuación Z (es decir, el valor del índice biométrico normalizado para la edad gestacional) por unidad de tiempo (conocida como velocidad Z)[132].

La velocidad de crecimiento fetal, típicamente representada como una desviación en las tablas de velocidad de crecimiento (cambio en percentiles o puntuación Z con el avance de la gestación), es particularmente relevante para evaluar el crecimiento fetal, más que el tamaño fetal en un momento determinado. Algunos estudios reportan que la reducción de la velocidad de crecimiento en el tercer trimestre se encuentra asociada con un incremento de ciertos RPA[15,130,133], pero no todos están de acuerdo con estas conclusiones.

Con respecto al valor de la velocidad de crecimiento como método diagnóstico de las alteraciones en el crecimiento, Sovio et al. en 2015[15] y 2018[134] y Deter et al. en 2017[135] informaron que la velocidad de crecimiento fetal o la desviación porcentual del crecimiento, independientemente del modelo de población utilizado (universal, local,

prescriptiva o descriptiva), es más relevante que el PFE para determinar los trastornos del crecimiento intrauterino[54].

Pero también hay autores que han relacionado el uso de la velocidad de crecimiento como método diagnóstico de RPA. Bligh et al. en 2019[92] sugirieron que algunos fetos exhiben una disminución sutil en la velocidad de crecimiento a término, lo que puede ser responsable del mayor riesgo de compromiso intraparto y aparición de RPA. De hecho, en los casos de los recién nacidos, se ha demostrado repetidamente que la velocidad de crecimiento en la primera infancia es un mejor predictor del peso subsiguiente que cualquier otra medida transversal[136]. McDonald et al.[133] informaron que la velocidad de crecimiento reducida con una disminución mayor de 35 percentiles entre las semanas 28 y 36 de gestación entre los fetos nacidos adecuados para la edad gestacional se asocia con indicadores prenatales, intraparto y neonatales de insuficiencia placentaria. En el artículo de Chatzakis et al.[137] una desaceleración del crecimiento fetal mayor o igual al percentil 50 en fetos no PEG se asoció con un mayor riesgo de ingreso en la UCI neonatales [Odds Ratio (OR) 1,8] y muerte perinatal (OR 3,8). Pacora et al.[138] encontraron que un feto con una disminución del percentil de peso mayor de 50 puntos tiene 4,7 veces más riesgo de muerte anteparto.

Por lo tanto, la observación en la caída del percentil o Z-score en las tablas de crecimiento, debería indicar una monitorización posterior[54]. Una caída de más de dos cuartiles (o más de 50 puntos de percentil) se interpreta como CIR, siendo éste un criterio recomendado por consenso[54,85].

Sin embargo, todavía hay autores que no apoyan estas consideraciones, como Ciobanu et al. en su estudio de 2019[82] en el que concluyeron que la adición de la velocidad de crecimiento estimada entre las 32 y 36 semanas de gestación no mejoró el diagnóstico de PEG al nacer ni el de aparición de RPA.

Por ello, la relación entre velocidad de crecimiento en un tiempo dado y la detección de fetos PEG en riesgo de resultados adversos, requiere investigaciones adicionales[54].

Biomarcadores

Los biomarcadores placentarios tienen un papel potencial en el cribado, diagnóstico y terapia de las enfermedades placentarias relacionadas con los trastornos hipertensivos del embarazo y/o el CIR[139]. Se han investigado varios factores placentarios, incluidas las proteínas placentarias, así como el microARN y el ARNm. Algunas proteínas placentarias, como la proteína plasmática A asociada al embarazo (PAPP-A), son biomarcadores de la función placentaria en el primer trimestre, aunque su capacidad de predicción es limitada[140,141].

- Factor de crecimiento placentario (PlGF) y la forma soluble de la tirosina quinasa-1 (sFlt-1): la insuficiencia uteroplacentaria se asocia con una angiogénesis desequilibrada, lo que resulta en una regulación al alza de sFlt-1 y una regulación a la baja de PlGF[142–144]. Los niveles anormales de factores angiogénicos se reflejan en la circulación materna y juegan un papel patogénico clave en el desarrollo de la disfunción endotelial subyacente a la preeclampsia[142,145]. El valor de los biomarcadores angiogénicos en la predicción y caracterización de la preeclampsia y CIR de inicio temprano ha sido demostrado en una gran cantidad de estudios[142,146].
  Diferentes estudios han demostrado consistentemente que PlGF medido en el primer trimestre es útil en la predicción de preeclampsia y/o CIR/PEG de inicio temprano[147–150]. En el segundo trimestre, tanto PlGF como sFlt-1 tienen un fuerte valor predictivo de preeclampsia y/o CIR de aparición temprana[151–154], pero una asociación con la preeclampsia y CIR de aparición tardía muy débil[151]. Sin embargo, cuando se determina en el tercer trimestre de gestación, valores más bajos de PlGF se relacionan con pacientes con fetos PEG o pacientes con resultado perinatal adverso en general[143,155–157], especialmente cuando se asocian con preeclampsia de inicio tardío[158].

  En el estudio de Lobmaier et al. en 2014 se evidenció que los factores angiogénicos, medidos en el momento del diagnóstico de PEG, pueden predecir un resultado adverso del embarazo, asociándose valores bajos de PlGF con dichos RPA[159]. En línea con los resultados de una publicación anterior que informa que, en fetos con una CA menor del percentil 10, PlGF identificó aquellos asociados con hallazgos placentarios

anormales, concluyendo que PlGF es útil para discriminar la "restricción del crecimiento intrauterino placentario" de los "fetos constitucionalmente pequeños"[160].

La relación del cociente entre el PlGF y la sFlt-1, se ha propuesto como un predictor a corto plazo para descartar la preeclampsia en las mujeres en las que se sospecha clínicamente esta condición[161]. Aunque algunos informes sugieren que el uso de la proporción entre sFlt-1/PlGF podría ser útil para el manejo y la diferenciación entre PEG y CIR[162–166], la falta de datos de ensayos de intervención impide recomendar estas pruebas como complemento de la ecografía.
Un reciente estudio de Hurtado et al. de junio de 2022[167] reporta que el cociente entre sFlt-1/PlGF es un buen predictor de RPA en el momento del diagnóstico de fetos CIR o PEG de inicio tardío y por lo tanto podría usarse para el asesoramiento prenatal de estos embarazos.

El hallazgo de que la relación sFlt-1 / PlGF puede predecir la presencia o ausencia a corto plazo de preeclampsia[161] abre la posibilidad de que los marcadores de proteínas placentarias puedan también ofrecer una prueba de detección considerablemente mejorada para distinguir al feto PEG sano del feto CIR mediada por placenta, en riesgo de muerte fetal y morbilidad relacionada con la asfixia.

- PAPP-A y la subunidad beta de gonadotropina coriónica humana (β-hCG): la evidencia reciente sugiere que las patologías subyacentes al CIR y PEG tienen lugar en el primer trimestre. Una evaluación más temprana, antes del establecimiento de la disfunción placentaria, puede tener el potencial de mejorar el tratamiento y el pronóstico en la práctica clínica[140]. La rentabilidad sería aún mayor si esta identificación pudiera ser un derivado del programa combinado de detección bioquímica y ecografía del primer trimestre ampliamente implementado para el síndrome de Down, que analiza los marcadores serológicos maternos de PAPP-A y la β-hCG[168]. Algunos estudios ya han evaluado la capacidad individual de PAPP-A y β-hCG para predecir fetos PEG. Estos estudios demuestran que estos marcadores tienen una influencia independiente en el peso final al nacer y correlacionan una menor PAPP-A con un mayor riesgo de que el feto desarrolle PEG. Sin embargo, su

poder predictivo es insuficiente para que se utilicen solos para la detección de PEG[169–172].

Modelos combinados predictivos

Se están diseñando modelos combinados que aumentan la capacidad predictiva de la ecografía básica en el tercer trimestre del embarazo para predecir PEG o seleccionar pacientes con riesgo de dar a luz fetos PEG de inicio tardío[18,22–24,118,173,174]. En algunos de estos estudios, se realiza una ecografía mucho antes del parto (semana 30-34)[22,25,118] en otros, se realizan varias ecografías a lo largo del tercer trimestre del embarazo, con el fin de evaluar longitudinalmente el crecimiento fetal[92]. En otros, se introduce el estudio Doppler o marcadores bioquímicos circulantes, como el PlGF y la sFlt-1, aumentando así la sensibilidad y especificidad, así como las tasas de detección de fetos PEG. Sin embargo, las estrategias anteriores no se realizan de forma rutinaria en embarazos de bajo riesgo[18,24,25,82,175–178].

Recientemente, se han publicado dos algoritmos en los que se combina la utilización de PFE por ecografía y el cociente sFlt-1/PlGF, que muestran un buen rendimiento para predecir resultados adversos en CIR de inicio temprano[179,180]. Sin embargo, pocos estudios han investigado el valor agregado de un modelo predictivo para la evaluación del riesgo individual en CIR y PEG de inicio tardío.

Miranda et al. 2017 utilizó un modelo predictivo combinado, incluyendo riesgo a priori (características maternas), PFE en el tercer trimestre (32 + 0 a 36 + 6), índice de pulsatilidad de Arteria uterina (IP AUt), PlGF y estriol (con lipocalina-2 para PEG), y logró una tasa de detección del 61 % para casos de PEG y del 77 % para CIR. El modelo combinado se desempeñó significativamente mejor que el uso de PFE solo ($p < 0,001$ y $p = 0,002$, respectivamente) donde encontraron tasas de detección del 52% para PEG y 64% para CIR respectivamente[181].

Ciobanu et al. reportaron una tasa de detección de 32% en la detección por factores maternos, 66% por factores maternos y PEF a las 35-36 semanas de gestación, y 69 % con la adición de biomarcadores [IP AUt, índice de pulsatilidad de la arteria umbilical, índice de pulsatilidad de la arteria cerebral media, PlGF y sFlt-1][82].

El último estudio publicado en 2022 sobre modelos combinados propone una nueva estrategia para la predicción de PEG que considera PEG como una condición de espectro bidimensional definida por la edad gestacional al momento del parto y el puntaje Z del peso al nacer para dicha edad gestacional[182–189]. Desarrollan un modelo de riesgos competitivos en el que incluyen además del PFE por ecografía a las 35-37 semanas de gestación, factores maternos y biomarcadores de placentación (PlGF e IP AUt). Al compararlo con el modelo tradicional de diagnóstico de PEG como PFE menor de 10 informan de una mejora del rendimiento predictivo para un recién nacido PEG con percentil por debajo de 3[190].

Con estos modelos se pretende identificar los embarazos que se beneficiarían de la monitorización intensiva del crecimiento fetal, el perfil biofísico y bioquímico, el patrón de frecuencia cardíaca fetal y los parámetros Doppler, con el objetivo de optimizar el plan de parto y elegir el nivel adecuado de atención neonatal. Esta estrategia debería conducir a una gestión eficaz centrada con los recursos mínimos necesarios[190].

2. OBJETIVOS

Una vez expuesto el conocimiento que se tiene hasta la actualizad sobre el tema de las alteraciones del crecimiento fetal y su diagnóstico prenatal y tras un estudio exhaustivo de la bibliografía disponible, se nos plantearon las siguientes preguntas:

- ¿cuál es el mejor modelo de crecimiento para predecir los RPA?
- ¿cuál es el mejor modelo de crecimiento para predecir recién nacidos GEG y PEG?
- ¿es la velocidad de crecimiento en el tercer trimestre de gestación un mejor parámetro para predecir RPA?
- ¿sería más útil utilizar para predecir un recién nacido PEG un modelo combinado que incluya datos de la ecografía del tercer trimestre de gestación, características maternas y marcadores bioquímicos utilizados para el cribado de anomalías cromosómicas en el primer trimestre de gestación (PAPP-A y β-HCG) que la biometría sola?

Es lo que tratamos de responder en los artículos que comprenden esta tesis y cuyos objetivos específicos son:

1. Evaluar la capacidad predictiva del PPE tanto por ecografía a las 35 semanas de embarazo como en el momento del parto para predecir RPA de acuerdo con 5 estándares de crecimiento fetal, que incluyen referencias poblacionales, personalizadas e internacionales: *Savirón-Cornudella R, Esteban L, M, Tajada-Duaso M, Castán-Mateo S, Dieste-Pérez P, Cotaina-Gracia L, Lerma-Puertas D, Sanz G, Pérez-López F, R: Detection of Adverse Perinatal Outcomes at Term Delivery Using Ultrasound Estimated Percentile Weight at 35 Weeks of Gestation: Comparison of Five Fetal Growth Standards. Fetal Diagn Ther 2020;47:104-114. doi: 10.1159/000500453*.

2. Evaluar la capacidad predictiva del PPE por ecografía a las 35 semanas de gestación para predecir un recién nacido GEG a término de acuerdo con 6 modelos de crecimiento, personalizados y no personalizados, locales e internacionales. El objetivo secundario es determinar su capacidad predictiva para detectar RPA y si el intervalo entre la ecografía y el parto influye en la tasa de detección de recién nacidos GEG: *Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, Dieste Pérez P, Pérez-López FR, Castán-Larraz B, Sanz G, Tajada-Duaso M. Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and*

Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards. Fetal Diagn Ther. 2021;48(1):15-23. doi: 10.1159/000510020

3. Evaluar la capacidad predictiva del PPE por ecografía a las 35 semanas de gestación para predecir PEG de inicio tardío según 6 estándares de crecimiento personalizados y no personalizados, locales e internacionales. El objetivo secundario es determinar si el intervalo de entre la ecografía y el parto influye en la tasa de detección de los recién nacidos PEG: *Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, Dieste-Pérez P, Pérez-López FR, Campillos JM, Castán-Larraz B, Sanz G, Tajada-Duaso M. Prediction of Late-Onset Small for Gestational Age and Fetal Growth Restriction by Fetal Biometry at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of Six Fetal Growth Standards. J Clin Med. 2021 Jul 3;10(13):2984. doi: 10.3390/jcm10132984*

4. Evaluar si la disminución del crecimiento fetal al final del tercer trimestre de gestación se asocia con la aparición de RPA y si esto sirve como un buen parámetro para predecirlos. Para ello hemos utilizado el percentil de peso en la ecografía de la semana 35 de gestación y el percentil de peso al nacer, asumiendo que la diferencia de percentiles entre ambos momentos sería un marcador subrogado de lo que realmente se puede medir, que es la diferencia de percentiles entre una ecografía próxima al parto y una ecografía en la semana 35: *Dieste Pérez P, Esteban LM, Savirón-Cornudella R, Pérez-López FR, Castán-Mateo S, Sanz G, Tajada-Duaso M. Reduced Growth in Non-Small for Gestational Age Fetuses from 35 Weeks of Gestation to Birth and Perinatal Outcomes. Fetal Diagn Ther. 2021;48(11-12):768-777. doi: 10.1159/000519639.*

5. Comparar la capacidad predictiva de neonatos PEG entre la biometría fetal realizada en la ecografía del tercer trimestre entre las 35 y 37 semanas de gestación y un modelo multivariante compuesto por la citada ecografía, características maternas y marcadores bioquímicos utilizados para el cribado de anomalías cromosómicas en el primer trimestre de gestación (PAPP-A y β-HCG): *Dieste-Pérez, P.; Savirón-Cornudella, R.; Tajada-Duaso, M.; Pérez-López, F.R.; Castán-Mateo, S.; Sanz, G.; Esteban, L.M. Personalized Model to Predict Small for Gestational Age at Delivery Using Fetal Biometrics, Maternal Characteristics, and Pregnancy Biomarkers: A Retrospective Cohort Study of Births Assisted at a Spanish Hospital. J. Pers. Med. 2022, 12, 762. https://doi.org/10.3390/jpm12050762*

3. TRABAJOS PUBLICADOS

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Detection of Adverse Perinatal Outcomes at Term Delivery Using Ultrasound Estimated Percentile Weight at 35 Weeks of Gestation: Comparison of Five Fetal Growth Standards

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Keywords

Adverse perinatal outcomes · Birth weight · Estimated fetal weight · Estimated percentile weight · Fetal growth standard · INTERGROWTH-21st · Ultrasound · World Health Organization

Abstract

Objective: To assess the predictive ability of the ultrasound estimated percentile weight (EPW) at 35 weeks of pregnancy to predict adverse perinatal outcomes (APOs) at term delivery according to 5 fetal growth standards, including population, population-customized, and international references. ***Methods:*** This was a retrospective cohort study of 9,585 singleton pregnancies. Maternal clinical characteristics, fetal ultrasound data obtained at 35 weeks and pregnancy and perinatal outcomes were used to calculate EPWs to predict APOs according to: the customized and noncustomized (NC) Miguel Servet University Hospital (MSUH), the customized Figueras, the NC INTERGROWTH-21st, and the NC World Health Organization (WHO) international standards. APOs were defined as the occurrence of cesarean or instrumental delivery for nonreassuring fetal status, 5-min Apgar score <7, arterial cord blood pH <7.10, or stillbirth. The predictive ability of EPW for APOs was analyzed using the area under the curve (AUC), and sensitivities were calculated for different false-positive rates (FPRs). ***Results:*** For a 10% FPR, detection rates for total APOs ranged between 12.7% with the customized MSUH (AUC 0.52; 95% CI 0.50–0.55) and 14.4% with the NC MSUH standard (AUC 0.55; 95% CI 0.53–0.57) for EPW by ultrasound; and from 22.0% with the customized MSUH standard (AUC 0.60; 95% CI 0.58–0.63) to 27.8% with the NC WHO (AUC 0.65; 95% CI 0.63–0.68) for EPW at delivery. ***Conclusions:*** The predictive capacity of the EPW for APOS is limited and similar, by both ultrasound and at delivery, for the 5 growth standards, without significant differences between customized and NC standards.

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Introduction

The prenatal detection of low birth weight risk is a challenging diagnostic task based on the third trimester estimated fetal weight (EFW) [1] by ultrasound. Small for gestational age (SGA) infants, those with a birth weight below the 10th percentile, and especially those with fetal growth restriction, have been associated with increased risk of adverse perinatal outcomes (APOs) [2]. These fetuses are the leading cause of stillbirth [3–5] and have more risks of both neonatal morbidity [6] and mortality [7]. Hence, the 10th percentile weight threshold point is considered a predictor of APOs [8].

Different fetal growth standards have been based on the EFW to calculate the estimated percentile weight (EPW) following the Hadlock et al. [9] methodology. These standards can also be customized to maternal and fetal physiological variables according to the Gardosi et al. [10] method. Customized standards have been proposed as better detectors of APOs than population-based standards (noncustomized [NC]) [11], although some studies have questioned the validity of customized standards [12, 13].

Fetal growth standards were developed using local populations [9, 14–16], and international population standards have recently been published by EFW, including those from the INTERGROWTH-21st project [17] and the World Health Organization (WHO) [18], whose differences have already been reported [19]. The INTERGROWTH-21st standard proposed use of the Stirnemann et al. [17] formula to estimate fetal weight instead of the classic and most used one of Hadlock et al. [20] III. According to the recent review by McCowan et al. [2], international population ultrasound standards still require more comparative studies for validation.

Since the controversy arose about the most appropriate method to predict the risk of APOs and the lack of comparative assessment for the cited approaches, the objective of this study is to compare the predictive ability of EPW according to 5 growth standards, either by ultrasound at 35 weeks or at delivery, including customized and NC growth standards, to predict APOs at term delivery.

Methods

Study Design

This was a retrospective cohort study of births assisted at the Miguel Servet University Hospital (MSUH), between March 2012 and December 2016. The inclusion criteria were as follows: (i) live singleton pregnancies controlled in MSUH from the first trimester of gestation; (ii) fetal ultrasound assessment at gestational age of 35 (range 34–36) weeks; and (iii) deliveries between 37 and 42 weeks of gestational age with fetuses without stillbirth associated with malformations or chromosomal abnormalities. The investigation was approved by the Clinical Research Ethics Committee of Aragon (PI 18/333).

The last menstrual period was adjusted by first trimester ultrasound [21]. Universal ultrasound screening was performed at 35 weeks (range 34–36 weeks) at the Ultrasound and Prenatal Diagnosis Unit using either an ultrasound machine Voluson 730 Expert, E6, E8 (General Electric, Healthcare, Zipf, Austria) or an Aloka Prosound SSD-5000 (Hitachi Aloka Medical Systems, Tokyo, Japan).

EFW was calculated with Hadlock et al. [20] formula III (biparietal diameter, cephalic circumference, abdominal circumference, and femur length) to estimate percentile weight because these EFWs were used for building the MSHU, Figueras et al. [14], and WHO standards. In addition, for the same reason, the Stirnemann et al. [17] formula (including only cephalic and abdominal circumference) was used to estimate percentile weight for INTERGROWTH-21st.

The variables included in the study were maternal age and body mass index (BMI) at the beginning of pregnancy, parity, maternal and paternal height, maternal ethnic origin, smoking habits, infant gender, birth weight, and ultrasound EFW. We also collected perinatal outcomes to analyze APOs defined as the occurrence of 5-min Apgar score <7, instrumental or cesarean delivery for nonreassuring fetal status (NRFS) [22], arterial cord blood pH <7.10, and stillbirth.

Estimated Percentile Weight

EPWs were calculated according to 5 different customized and NC growth standards including population, population-customized, and international references. For the customized ones, the Gardosi et al. [10] methodology was used for (i) the MSUH standard [16] based on parity, age, BMI and maternal height, paternal height, and fetal gender (Saviron-Cornudella et al. [16]). These growth charts were built using a modified version of Hadlock et al. [9] growth charts adjusted to our population with a coefficient of variation that changes with gestational age (ii) the Barcelona Clinic Hospital (Figueras et al. [14]). For the NC standards, we used (iii) a NC version of the MSUH standard (Saviron-Cornudella et al. [16]); (iv) the international population INTERGROWTH–21st standard, performed in low-risk pregnancies at delivery (>37 weeks) [23] by EFW (<37 weeks) [17]; and (v) the WHO fetal growth standard [18].

EPWs at delivery were estimated between 37 and 42 weeks of gestational age with the exception of the WHO growth standards analyzed only in the interval 37–39 as recommended by the WHO study authors [18] and by interpolation of 5, 10, 25, 50, 75, 90, and 95 percentiles estimated by quartile regression standards.

Statistical Analyses

Data were extracted, and differences between the groups with and without APOs were analyzed using the Mann-Whitney test or the chi-square test, as appropriate. The predictive ability of EPW provided by the 5 standards to diagnose APOs was analyzed using the area under the receiver-operating characteristic curve (AUC), comparing different AUCs with the DeLong et al. [24] method. Sensitivity (detection rate) was established for false-positive rates

(FPR) of 5, 10, 15, and 20%, respectively. The percentile threshold point corresponding to the FPR values was also calculated. In addition, a subanalysis was performed using a logistic regression model to estimate the OR and 95% CIs of the EPW as a predictor for APOs at delivery. Nonlinear dependences were explored using restricted cubic splines. The Kolmogorov-Smirnov test was used to compare the percentile distributions provided by Hadlock et al. [20] and Stirnemann et al. [17] formulas to calculate EFW with INTERGROWTH-21st standard.

The threshold *p* value was set at 0.05. Analyses were performed using R version 3.3.2 language programming (R Foundation for Statistical Computing, Vienna, Austria) [25].

Results

Comparisons of Infants with and without APOs

A total of 9,585 pregnant women were included in the present study. Table 1 shows their descriptive characteristics. Women with APOs (n = 645), (i) were older (p = 0.015), (ii) with higher rate of nulliparity and higher first trimester BMI (p = 0.001), and (iii) of lower height, (p < 0.001) as compared to controls (n = 8,940). APOs were more prevalent among male infants (55.8%; p = 0.025), and mean birth weight was lower in cases than in controls (p < 0.001). Regarding APOs, the prevalence was 6.6% in the entire population, infants with a 5-min Apgar score <7 represented 0.4%, percentages of instrumental or cesarean deliveries for NRFS were, respectively, 1.7 and 2.8%, arterial cord blood pH <7.10 2.6%, and stillbirth 0.2%.

Table 1 also displays medians and interquartile ranges among groups for the 5 studied standards for EFWs by ultrasound and weights at delivery and EPWs. There were lower percentile medians and interquartile ranges in cases with APOs as compared to controls for all the standards as calculated with ultrasound ($p \leq 0.042$) or at delivery (p < 0.001). EPW distributions are detailed in Figure 1, where a comparison of boxplots is shown for each standard. For the uncomplicated pregnancies, the EPW distribution shows quartiles near to 25 and 75% and medians around 50%, with the exception of the Figueras et al. [14] (59.5%) and the WHO (43.3%) standards that show, respectively, an overestimation and an underestimation of the expected value (50%). At delivery, the EPW distributions for all the standards were close to expected values in this group (50%) except for an underestimation of the WHO standard (median value 32.7%).

Table 2 shows the percentile distribution of the INTERGROWTH-21st standard analyzed using the Stirnemann et al. [17] or Hadlock et al. [20] formula to calculate EFW by ultrasound and how the Hadlock et al. [20] formula overestimates EPW with the INTERGROWTH-21st standard (p < 0.001).

Comparison of Growth Standards

Table 3 displays values of AUCs and sensitivities plus the percentile threshold point for different FPR to predict total APOs by ultrasound. For a 10% FPR, the detection rates for total APOs for all standards ranged between 12.7% with the customized MSUH (AUC 0.52; 95% CI 0.50–0.55) to 14.4% with the NC MSUH standard (AUC 0.55; 95% CI 0.53–0.57). These values were obtained with percentile threshold points below 12.4, 12.4, 18.5, 12.9, and 7.8% for, respectively, both NC and customized MSUH, Figueras et al. [14], INTERGROWTH-21st, and WHO standards. For a 20% FPR, the detection rates were between 24 and 26%, using 23.5, 23.8, 30.7, 23.5, and 15.5% as percentile threshold points.

Table 4 displays the same values of prediction of APOs as Table 3 but using EPW at delivery. For a 10% FPR, the detection rates for total APOs for all the standards ranged from 22.0% with the customized MSUH standard (AUC 0.60; 95% CI 0.58–0.63) to 27.8% with the WHO (AUC 0.65; 95% CI 0.63–0.68). These values were obtained considering as SGA percentiles below 11.9, 10.5, 11.9, 15.7% and under 5% for, respectively, both NC and customized MSUH, Figueras et al. [14], INTERGROWTH-21st, and WHO standards. For a 20% FPR detection rates ranged from 34 to 41%, using 21.6, 21.2, 22.7, 27.1, and 9.1% as percentile threshold points.

Figure 2 illustrates the receiver-operating characteristic curves comparison and AUC for the prediction of total APOs for the 5 standards estimated either by ultrasound at 35 weeks or at term delivery.

Figure 3 displays the results of the logistic regression model with the ORs and 95% CIs to predict APOs, both by ultrasound and at delivery, by EPW according to the 5 studied standards. Evaluations showed that lower percentiles were associated with higher risks of total APOs.

EPW by ultrasound was the only statistically significant common endpoint for the 5 studied standards to predict cesarean delivery for NRFS ($p \leq 0.009$) and total APOs ($p \leq 0.039$), ORs ranged between 0.994 (95% CI 0.991–0.997; p < 0.001) with the NC MSUH and 0.998 (95% CI 0.994–0.999; p = 0.039) with the customized MSUH standard. EPW at delivery was statistically significant for studied standards (except for stillbirth) in order to predict 5-min Apgar score <7 ($p \leq 0.042$–0.001), instrumental delivery (p < 0.001), cesarean section (p < 0.001), and arterial cord blood pH < 7.10 (p < 0.001) and

Table 1. Parental baseline characteristics (**a**), pregnancy (**b**), and perinatal characteristics (**c**) of uncomplicated pregnancies and pregnancies with APOs

Clinical characteristics	Uncomplicated pregnancies (n = 8,940)	Pregnancies with APOs (n = 645)	*p value**
a. *Parental characteristics*			
Maternal age, years	33.3 (30.1–36.0)	33.8 (30.2–36.5)	0.015
Maternal BMI, kg/m^2	23.2 (21.1–26.1)	23.9 (21.5–27.5)	<0.001
Maternal height, cm	163 (160–168)	162 (158–167)	<0.001
Paternal height, cm	176 (172–181)	176 (170–181)	0.262
Parity			
0	4,608 (51.5)	469 (72.7)	<0.001
1	3,579 (40.0)	145 (22.5)	
≥2	753 (8.5)	31 (4.8)	
Maternal ethnicity			
Caucasic	8,616 (96.4)	627 (97.2)	0.240
Asian	107 (1.2)	3 (0.5)	
African	211 (2.4)	15 (2.3)	
Maternal smoking habits			
Yes	1,438 (16.1)	108 (16.7)	0.701
No	7,502 (83.9)	537 (83.3)	
b. *Ultrasound parameters at 35 (34–36) weeks*			
Gestational age (weeks) at ultrasound	35.1 (35.0–35.3)	35.1 (35.0–35.3)	0.998
Estimated fetal weight (g) by Hadlock	2,497 (2319–2699)	2,440 (2253–2659)	<0.001
Estimated fetal weight (g) by Stirnemann	2,424 (2215–2651)	2,375 (2149–2609)	<0.001
Pc by standard	P50 (P10–P90)	P50 (P10–P90)	
MSUH NC	53.1 (12.4–93.4)	44.1 (8.2–90.3)	<0.001
Customized MSUH	53.0 (12.4–93.0)	50.2 (10.3–91.7)	0.042
Figueras	59.5 (18.5–93.6)	54.6 (13.7–91.8)	0.005
INTERGROWTH-21st	52.1 (12.9–89.9)	47.5 (8.6–87.1)	<0.001
WHO	43.4 (7.8–74.9)	40.5 (4.5–74.7)	0.005
c. *Pregnancy and perinatal outcomes*			
Gestational age at delivery	40.0 (39.1–40.7)	40.1 (39.1–40.9)	0.004
Newborn gender			
Female	4,367 (48.8)	285 (44.2)	0.025
Male	4,573 (51.2)	360 (55.8)	
Birth weight	3,325 (3,050–3,600)	3,180 (2,850–3,490)	<0.001
Pc by standard	P50 (P10–P90)	P50 (P10–P90)	
MSUH NC	53.1 (12.4–93.4)	35.9 (3.3–86.2)	<0.001
Customized MSUH	53.9 (10.5–93.4)	39.1 (3.2–88.8)	<0.001
Figueras	49.9 (11.9–89.8)	35.4 (3.6–83.2)	<0.001
INTERGROWTH-21st	52.1 (12.9–89.9)	38.5 (4.2–83.6)	<0.001
WHO	32.7 (4–74.7)	14.3 (4–73.0)	<0.001
5-min Apgar score <7	0	42	
Instrumental delivery for NRFS	0	161	
Cesarean delivery for NRFS	0	265	
Arterial cord blood pH <7.10	0	254	
Stillbirth	0	19	

* Comparison of uncomplicated pregnancies with pregnancies with APOs.

Data are reported as n (%) or medians (interquartile range).

MSUH, Miguel Servet University Hospital; NRFS, nonreassuring fetal status; WHO, World Health Organization; APOs, adverse perinatal outcomes; NC, noncustomized; BMI, body mass index; Pc, percentile.

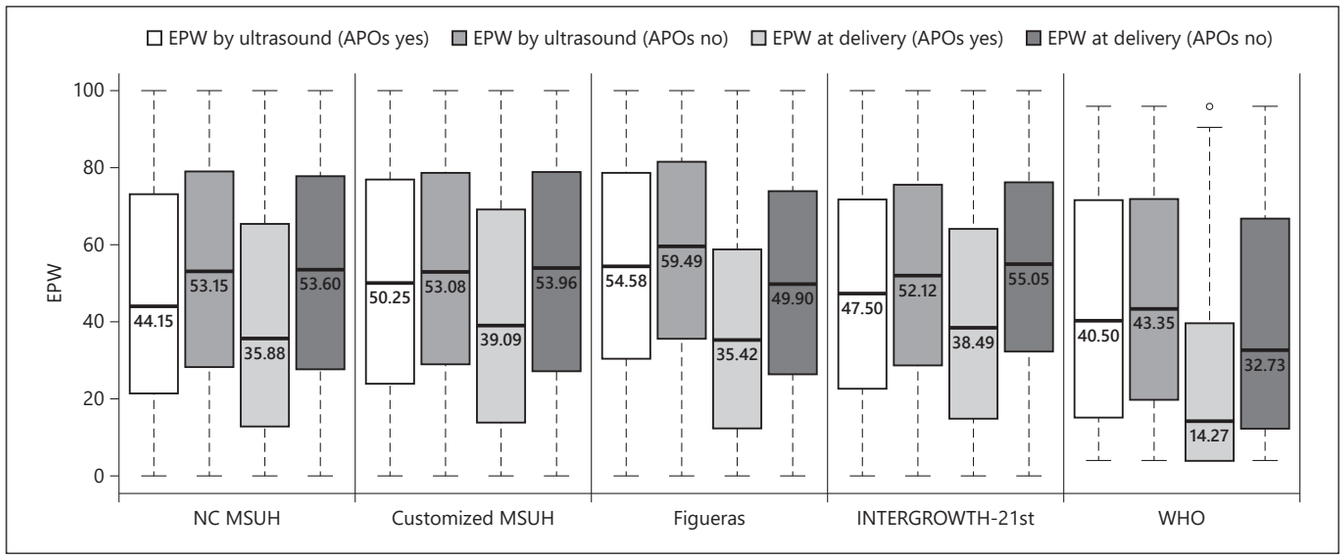

Fig. 1. Median and interquartile range of EPW boxplot comparison by ultrasound and at delivery of pregnancies with APOs and uncomplicated pregnancies. EPW, estimated percentile weight; MSUH, Miguel Servet University Hospital; WHO, World Health Organization; APOs, adverse perinatal outcomes; NC, noncustomized.

Table 2. Comparison of Pc distribution of INTERGROWTH-21st standard using Stirnemann et al. [17] or Hadlock et al. [20] formulas to estimate ultrasound fetal weight using the Kolmogorov-Smirnov test

EFW formula by	Pc 5	Pc 10	Pc 25	Pc 50	Pc 75	Pc 90	Pc 95
Hadlock et al. [20] method, %	14.1	23.3	40.1	60.4	78.9	90.2	94.7
Stirnemann et al. [17] method, %	6.2	12.7	28.3	51.9	75.5	89.8	94.9

Kolmogorov-Smirnov test ($p < 0.001$).
Pc, percentile; EFW, estimated fetal weight.

their sum (total APOs; $p < 0.001$) ORs ranged between 0.981 (95% CI 0.976–0.986; $p < 0.001$) with the WHO and 0.988 (95% CI 0.986–0.990; $p < 0.001$) with the customized MSUH standard (Fig. 3).

Nonlinear dependences between APO and EPW were explored for the 5 standards; those models were compared with linear models using AUC, but nonstatistically significant differences with linear models were found ($p > 0.05$).

Discussion

We have demonstrated the utility of EPW as a predictor of APOs in a large population of singleton pregnant women studied by ultrasound at 35 weeks and delivering at term. Second, the comparison of 5 growth standards showed a similar poor predictive ability for APOs, without significant differences between customized and NC standards and without any statistically significant advantage with any studied standard. We also found an overestimation of EPW with the Figueras et al. [14] standard by ultrasound and an underestimation with the WHO standard both by ultrasound and at delivery. However, their predictive abilities were similar to other standards after adjusting the percentile threshold point. We noted that the method to calculate the EPW by the WHO standard could introduce a lack of calibration in EPW, but it does not represent a loss in the discrimination ability. In addition, our population may differ from the WHO [18] standard in a similar way as shown in a recent study [19].

The Royal College of Obstetricians and Gynaecologists [26] recommends the use of customized birth weight

Table 3. AUROC and sensitivity analyses to detect APOs using EPW by ultrasound at 35 weeks (range 34–36 weeks) for different FPR percentages

Prediction of APOs using ultrasound EPW	AUC (95% CI)	Sensitivity and threshold Pc points*			
		FPR 5%	FPR 10%	FPR 15%	FPR 20%
5-min Apgar score <7					
NC MSUH	0.61 (0.51–0.70)	16.7 (Pc 5.7)	23.8 (Pc 12.1)	28.6 (Pc 17.7)	38.1 (Pc 23.2)
Customized MSUH	0.58 (0.49–0.68)	11.9 (Pc 6.0)	19.0 (Pc 12.3)	31.0 (Pc 17.9)	35.7 (Pc 23.6)
Figueras	0.59 (0.50–0.68)	11.9 (Pc 10.1)	16.7 (Pc 18.2)	26.2 (Pc 24.5)	35.7 (Pc 30.3)
INTERGROWTH-21st	0.60 (0.50–0.69)	11.9 (Pc 6.3)	19.0 (Pc 12.8)	26.2 (Pc 18.0)	35.7 (Pc 23.2)
WHO	0.61 (0.52–0.71)	15.3 (Pc<5)	26.2 (Pc 7.6)	31.0 (Pc 11.6)	38.1 (Pc 15.2)
Instrumental delivery for NRFS					
NC MSUH	0.55 (0.51–0.60)	3.7 (Pc 5.6)	13.0 (Pc 12.1)	17.4 (Pc 17.6)	22.4 (Pc 23.2)
Customized MSUH	0.53 (0.49–0.57)	3.7 (Pc 5.9)	8.1 (Pc 12.3)	15.5 (Pc 17.9)	21.1 (Pc 23.5)
Figueras	0.54 (0.49–0.58)	5.0 (Pc 10.1)	10.6 (Pc 18.2)	17.4 (Pc 24.5)	23.6 (Pc 36.3)
INTERGROWTH-21st	0.55 (0.51–0.59)	5.0 (Pc 6.2)	9.3 (Pc 12.7)	16.8 (Pc 18.0)	21.1 (Pc 23.2)
WHO	0.53 (0.48–0.57)	7.0 (Pc 5)	11.8 (Pc 7.5)	19.3 (Pc 11.6)	24.8 (Pc 15.2)
Cesarean delivery for NRFS					
NC MSUH	0.58 (0.54–0.61)	12.8 (Pc 5.8)	18.5 (Pc 12.3)	27.5 (Pc 18.0)	32.8 (Pc 23.5)
Customized MSUH	0.54 (0.51–0.58)	10.6 (Pc 6.1)	17.7 (Pc 12.5)	26.0 (Pc 18.2)	30.6 (Pc 23.8)
Figueras	0.56 (0.52–0.60)	12.1 (Pc 10.4)	17.4 (Pc 18.4)	25.3 (Pc 24.7)	32.1 (Pc 30.6)
INTERGROWTH-21st	0.56 (0.52–0.60)	12.1 (Pc 6.5)	17.4 (Pc 12.9)	26.0 (Pc 18.2)	25.9 (Pc 23.5)
WHO	0.56 (0.52–0.60)	12.2 (Pc 5)	17.8 (Pc 7.7)	24.2 (Pc 11.7)	29.1 (Pc 15.3)
Arterial cord blood pH <7.10					
NC MSUH	0.53 (0.49–0.57)	6.3 (Pc 5.7)	12.2 (Pc 12.1)	18.9 (Pc 17.8)	25.2 (Pc 23.3)
Customized MSUH	0.50 (0.47–0.54)	6.7 (Pc 6)	10.6 (Pc 12.3)	15.3 (Pc 17.9)	20.1 (Pc 23.5)
Figueras	0.52 (0.48–0.55)	7.1 (Pc 10.2)	12.2 (Pc 18.2)	15.7 (Pc 24.4)	21.3 (Pc 30.3)
INTERGROWTH-21st	0.48 (0.44–0.51)	2.4 (Pc 4.6)	7.1 (Pc 10.0)	10.2 (Pc 16.2)	16.1 (Pc 18.1)
WHO	0.51 (0.48–0.55)	6.3 (Pc 5)	13.0 (Pc 7.6)	17.7 (Pc 11.6)	21.7 (Pc 15.2)
Stillbirth					
NC MSUH	0.62 (0.46–0.79)	26.3 (Pc 5.7)	36.8 (Pc 12.1)	36.8 (Pc 17.6)	52.6 (Pc 23.2)
Customized MSUH	0.62 (0.46–0.78)	21.1 (Pc 6.0)	31.6 (Pc12.3)	36.8 (Pc 17.9)	47.4 (Pc 23.5)
Figueras	0.61 (0.45–0.71)	21.1 (Pc 10.1)	31.6 (Pc 18.2)	36.8 (Pc 24.5)	47.4 (Pc 30.3)
INTERGROWTH-21st	0.61 (0.45–0.77)	21.1 (Pc 7.0)	31.6 (Pc 13.0)	36.8 (Pc 19.0)	47.4 (Pc 24.0)
WHO	0.64 (0.50–0.79)	21.1 (Pc 5)	31.6 (Pc 7.5)	36.8 (Pc 11.6)	36.8 (Pc 15.2)
Total adverse perinatal outcomes					
NC MSUH	0.55 (0.53–0.57)	8.2 (Pc 5.8)	14.4 (Pc 12.4)	21.4 (Pc 18.0)	26.8 (Pc 23.5)
Customized MSUH	0.52 (0.50–0.55)	7.0 (Pc 6.0)	12.7 (Pc 12.4)	19.4 (Pc 18.2)	24.2 (Pc 23.8)
Figueras	0.53 (0.51–0.56)	7.9 (Pc 10.4)	13.3 (Pc 18.5)	19.4 (Pc 24.7)	25.3 (Pc 30.7)
INTERGROWTH-21st	0.54 (0.52–0.57)	7.9 (Pc 6.5)	13.0 (Pc 12.9)	20.9 (Pc 19.0)	25.9 (Pc 23.5)
WHO	0.53 (0.51–0.56)	8.4 (Pc 5)	13.8 (Pc 7.8)	20.5 (Pc 11.8)	25.1 (Pc 15.5)

* Sensitive threshold Pc: point that corresponds to a FPR.

EPW, estimated percentile weight; FPR, false-positive rate; MSUH, Miguel Servet University Hospital; NRFS, nonreassuring fetal status; Pc, percentile; WHO, World Health Organization; AUROC, area under the receiver-operating characteristic curve; APOs, adverse perinatal outcomes; AUC area under the curve; NC, noncustomized.

curves to identify SGA, and the adjustment of fetal weight should be individually performed and not by population. According to our results, customizing by ultrasound regarding the EPW does not increase the identification of APOs.

Prediction of APOs by Ultrasound

Figueras et al. [14] and MSHU [16] standards were developed following the Hadlock et al. [9] methodology although in MSHU we made modifications in the coefficients of variations and exponential growth

Table 4. AUROC and sensitivity analyses to detect APOs using EPW at delivery (37–42 weeks) for different FPR percentages

Prediction of APOs using EPW at delivery	AUC (95% CI)	Sensitivity and threshold Pc points*			
		FPR 5%	FPR 10%	FPR 15%	FPR 20%
5-min Apgar score <7					
NC MSUH	0.62 (0.60–0.65)	15.3 (Pc 6.3)	24.0 (Pc 11.9)	30.7 (Pc 17.2)	38.0 (Pc 22.7)
Customized MSUH	0.60 (0.58–0.62)	14.0 (Pc 5.7)	22.0 (Pc 10.5)	27.6 (Pc 15.9)	34.4 (Pc 21.2)
Figueras	0.62 (0.59–0.64)	15.7 (Pc 7.0)	24.7 (Pc 11.9)	29.9 (Pc 16.6	35.3 (Pc 21.6)
INTERGROWTH-21st	0.63 (0.61–0.66)	16.9 (Pc 9.2)	27.1 (Pc 15.7)	32.7 (Pc 21.4)	38.0 (Pc 27.1)
WHO	0.65 (0.63–0.68)	13.9 (Pc<5)	27.8 (Pc<5)	33.7 (Pc 6.7)	41.3 (Pc 9.1)
Instrumental delivery for NRFS					
NC MSUH	0.66 (0.61–0.70)	13.7 (Pc 5.9)	22.4 (Pc 11.6)	33.5 (Pc 16.7)	42.9 (Pc 22.0)
Customized MSUH	0.64 (0.59–0.68)	9.9 (Pc 5.2)	17.4 (Pc 9.9)	23.0 (Pc 15.3)	37.9 (Pc 20.5)
Figueras	0.65 (0.61–0.69)	11.8 (Pc 10.1)	23.0 (Pc 18.2)	31.7 (Pc 24.5)	42.9 (Pc 30.3)
INTERGROWTH-21s[t]	0.66 (0.62–0.71)	16.8 (Pc 8.5)	29.2 (Pc 15.0)	35.4 (Pc 20.6)	39.8 (Pc 26.3)
WHO	0.66 (0.59–0.73)	11.4 (Pc<5)	22.8 (Pc<5)	29.3 (Pc 6.4)	46.6 (Pc 8.7)
Cesarean delivery for NRFS					
NC MSUH	0.63 (0.59–0.67)	19.6 (Pc 6.1)	29.0 (Pc 11.5)	34.3 (Pc 16.7)	40.0 (Pc 22.0)
Customized MSUH	0.60 (0.56–0.64)	17.7 (Pc 5.4)	26.4 (Pc 10.1)	32.1 (Pc 15.5)	36.2 (Pc 20.5)
Figueras	0.62 (0.58–0.66)	20.4 (Pc 6.6)	27.9 (Pc 11.4)	33.6 (Pc 16.2)	37.4 (Pc 21.1)
INTERGROWTH-21st	0.63 (0.60–0.67)	18.9 (Pc 8.6)	28.7 (Pc 15.1)	36.6 (Pc 20.7)	40.4 (Pc 26.5)
WHO	0.66 (0.61–0.72)	16.5 (Pc<5)	33.0 (Pc<5)	39.2 (Pc 6.5)	44.2 (Pc 8.8)
Arterial cord blood pH <7.10					
NC MSUH	0.58 (0.55–0.62)	11.4 (Pc 5.9)	18.5 (Pc 11.3)	22.8 (Pc 16.4)	30.7 (Pc 21.8)
Customized MSUH	0.56 (0.52–0.60)	11.8 (Pc 5.2)	17.3 (Pc 10.0)	22.4 (Pc 15.3)	27.6 (Pc 20.4)
Figueras	0.58 (0.55–0.62)	12.6 (Pc 10.2)	18.9 (Pc 18.2)	22.0 (Pc 24.4)	27.2 (Pc 30.3)
INTERGROWTH-21st	0.59 (0.56–0.63)	12.2 (Pc 8.5)	18.6 (Pc 14.9)	24.4 (Pc 20.6)	31.9 (Pc 26.3)
WHO	0.62 (0.57–0.68)	11.2 (Pc<5)	22.4 (Pc<5)	29.5 (Pc 6.4)	35.7 (Pc 8.7)
Stillbirth					
NC MSUH	0.59 (0.44–0.73)	15.8 (Pc 5.7)	26.3 (Pc 11.1)	31.6 (Pc 16.1)	31.6 (Pc 21.5)
Customized MSUH	0.61 (0.46–0.75)	21.1 (Pc 5.1)	26.3 (Pc 9.8)	31.6 (Pc 15.2)	36.8 (Pc 20.1)
Figueras	0.59 (0.44–0.73)	15.8 (Pc 6.2)	21.1 (Pc 10.9)	26.3 (Pc 15.7)	31.6 (Pc 21.5)
INTERGROWTH-21st	0.56 (0.41–0.71)	15.8 (Pc 8.3)	15.8 (Pc 14.7)	26.3 (Pc 20.1)	26.3 (Pc 26.0)
WHO	0.61 (0.42–0.80)	14.6 (Pc<5)	29.1 (Pc<5)	33.3 (Pc 6.3)	33.3 (Pc 8.5)
Total adverse perinatal outcomes					
NC MSUH	0.62 (0.60–0.65)	15.3 (Pc 6.3)	24.0 (Pc 11.9)	30.7 (Pc 17.2)	38.0 (Pc 22.7)
Customized MSUH	0.60 (0.58–0.62)	14.0 (Pc 5.7)	22.0 (Pc 10.5)	27.6 (Pc 15.9)	34.4 (Pc 21.2)
Figueras	0.62 (0.59–0.64)	15.7 (Pc 7.0)	24.7 (Pc 11.9)	29.9 (Pc 16.6)	35.3 (Pc 21.6)
INTERGROWTH-21st	0.63 (0.61–0.66)	16.9 (Pc 9.2)	27.1 (Pc 15.7)	32.7 (Pc 21.4)	38.0 (Pc 27.1)
WHO	0.65 (0.63–0.68)	13.9 (Pc<5)	27.8 (Pc<5)	33.7 (Pc 6.7)	41.3 (Pc 9.1)

* Sensitive threshold Pc: point that corresponds to a FPR.

EPW, estimated percentile weight; FPR, false-positive rate; MSUH, Miguel Servet University Hospital; NRFS, nonreassuring fetal status; Pc, percentile; WHO, World Health Organization; AUROC, area under the receiver operating characteristic curve; AUC, area under the curve; APOs, adverse perinatal outcomes; NC, noncustomized.

model to build a standard that can explain the differences in EPW by ultrasound. It is important to highlight that the Stirnemann et al. [17] formula includes only cephalic and abdominal circumferences to calculate the EFW used in the INTERGROWTH-21st standard for calculating the EPW, which would introduce a bias, in contrast to the Hadlock et al. [20] III formula.

Contemporary series of ultrasound measurements in the 34th week or above of gestational age found values of AUC <0.60 and sensitivities in the range of 15–20% (FPR 10%) to detect APOs [27–29]. Moreover, recent studies

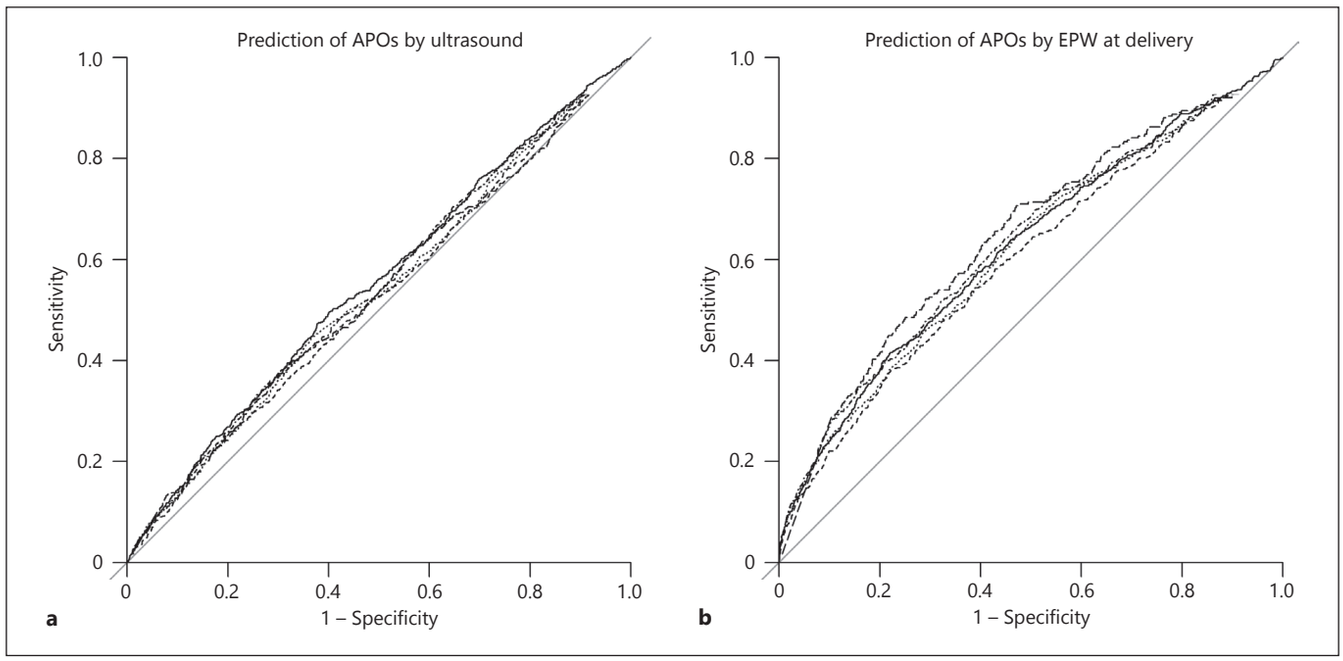

Fig. 2. Receiver-operating characteristic curves: comparison of fetal growth standards and AUC (ORs and 95% CIs) for prediction of total APOs using EPW by ultrasound at 35 weeks (**a**) and at term delivery (**b**). Growth standards: NC MSUH [16] (––––), Customized MSUH [16] (– – –), Figueras et al. [14] (· · · · ·), INTERGROWTH-21st [17] (– · – · –), WHO [18] (– · · · –). APOs, adverse perinatal outcomes; EPW, estimated percentile weight.

have shown that an early diagnosis of SGA in the third trimester can help to reduce APOs, reflecting the benefit of prenatal diagnosis in these cases [3, 30]. Our present study performed at 35 weeks also showed a poor discriminative ability and low detection rate of APOs; however, the logistic regression model showed that a lower percentile by ultrasound was a risk factor for APOs. Hua et al. [31] concluded in a comparison that 3 fetal growth standards (INTERGROWTH-21st, National Institute of Child Health and Human Development, and WHO fetal growth standards) provided limited accuracy for identifying fetuses at risk of APOs, but the analysis among women enrolled in the RADIUS trial between November 1987 and May 1991 and ultrasounds measurements under 35 weeks.

Ganzevoort et al. [32], also in 2018, suggested that the use of dichotomization at the 10th percentile to define normal versus abnormal fetal growth was a limitation for ultrasound as a single diagnostic test to predict APOs. According to our results, although an increase of the cutoff percentile point by ultrasound would improve the detection rate of APOs, it would also increase both the FPR and the number of unnecessary tests performed.

Sovio et al. [27] reported a comparative selected and universal ultrasound blinded analysis of detection of APOs in nulliparous women but only in SGA with an EPW calculated with a population and a customized standard in pregnant women with a clinically indicated scan provided latter at 26 and 36th weeks and including preterm deliveries. They conclude that customization did not increase the strength of association between SGA and neonatal morbidity compared with NC. Our study compares the standards for all fetuses (SGA and non-SGA) but with an ultrasound performed universally at 35 weeks and deliveries at term and found similar results to SGA cases, without any significant difference between customized and NC growth standards. Therefore, our results show that even with an accurate prediction of percentile weight, the prediction of APOs could not be perfect because many factors other than estimate percentile weight can influence outcome.

Prediction of APOs at Delivery

Sovio et al. [33] recently reported that EPW at delivery, used in both customized and NC standards, provided values of AUC <0.60 and sensitivities of 15–20% FPR (10%). They concluded that the diagnostic abilities of these stan-

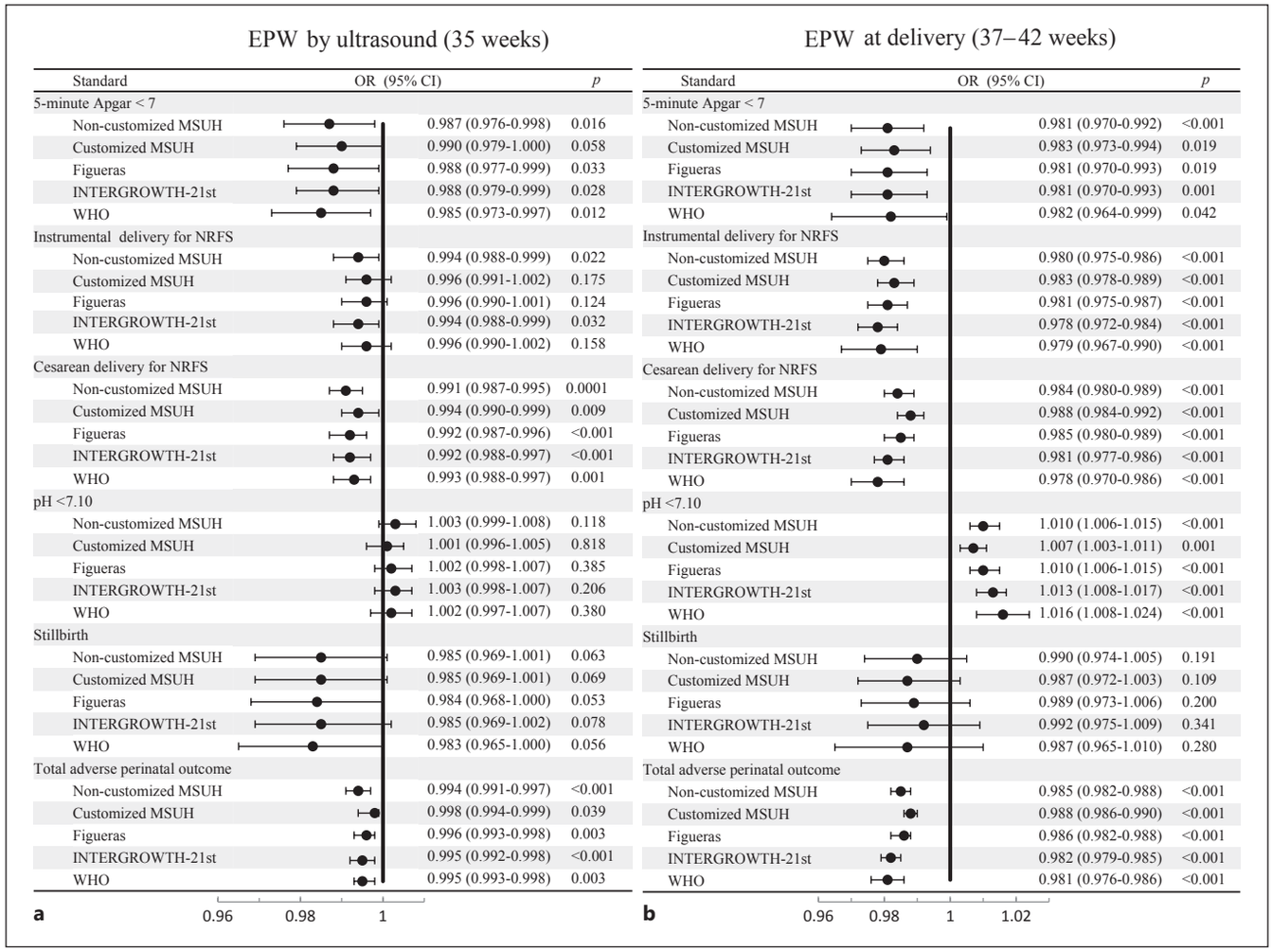

Fig. 3. ORs 95% CIs and *p* values of standards in order to predict APOs according to EPW by ultrasound (**a**) and at delivery (**b**). NRFS, nonreassuring fetal status; MSUH, Miguel Servet University Hospital; WHO, World Health Organization; EPW, estimated percentile weight.

dards to detect APOs were poor, although SGA infants were associated with risk of APOs. In our study, we observed significant differences in median values of weight and EPW at delivery between uncomplicated pregnancies and those that developed APOs for the 5 standards analyzed and independent of customization, with sensitivities and AUC values for detecting APOs slightly above those of Sovio et al. [33].

In 2018, Iliodromiti et al. [34] recommended that the cutoff points for the detection of APOs must be increased to the 25th percentile at delivery, since the 10th percentile has been considered as very restrictive, regardless of whether the standard is customized (partially) or not. We found that EPW at delivery is significantly associated with APOs, although our results show that the 10th percentile threshold point at delivery to predict APOs is also limited. It can also be concluded that the ability to predict APOs of the weight percentile increases when the estimation of the weight assessment is performed closer to delivery.

Strengths and Limitations of the Study

Our investigation has several strengths, including the sample size, which is important since a large number of women are needed due to the low prevalence of APOs and with the comparison including population, population-customized, and international references. To the best of our knowledge, this is the first time that EPWs were studied with 2 EFW calculation formulas (Hadlock et al. [20]

and Stirnemann et al. [17]). Since the Hadlock et al. [20] formula overestimates EPW with the INTERGROWTH-21st standard, the Stirnemann et al. [17] formula may be recommendable to calculate EFW using this standard. The main limitation of our investigation is that the information of the ultrasound was available to the obstetricians which could mean a bias in the management of the pregnancies although the lowest percentiles are detected by all the standards.

Research has been developed to increase the detection of total APOs by other maternal and fetal risk variables in addition, or not, to the EFW and EPW, such as the Doppler study, maternal characteristics or other biometric, biophysical or biochemical variables [28, 29, 35–39] although with limited results. Further studies that combine the different approaches are required.

Clinical Relevance

In summary, the predictive capacity of the EPW for APOs is similar, and limited, for ultrasound EFW at 35 weeks and for fetal weight at delivery at term, for the 5 growth standards, without significant differences between customized and NC standards. It seems likely that the procedures selected to calculate EPW are less relevant than previously believed and the 10th percentile threshold point is limited for the prediction of APOs, especially by ultrasound assessment.

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Statement of Ethics

The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.S.-C., L.M.E., and L.C.-G.: contributed to the conception of the study. R.S.-C., L.M.E., M.T.-D., S.C.-M., L.C.-G., D.L.-P., G.S., and F.R.P.-L.: contributed to the design of the work. R.S.-C., L.C.G., D.L.-P., and P.D.-P.: carried out data acquisition, and R.S.-C. and L.M.E.: performed statistical analysis. All authors were involved in the interpretation of the study results, as well as the drafting and revision of the manuscript, and all approved the final version to be published.

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Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards

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Keywords

Adverse perinatal outcomes · Large for gestational age · Birth weight · Estimated fetal weight · Estimated percentile weight · Fetal growth standard · INTERGROWTH-21st · Ultrasound · WHO fetal growth charts

Abstract

Objective: The aim of the study was to assess the predictive ability of the ultrasound estimated percentile weight (EPW) at 35 weeks to predict large for gestational age (LGA) at term delivery according to 6 growth standards, including population, population-customized, and international references. The secondary objectives were to determine its predictive ability to detect adverse perinatal outcomes (APOs) and whether the ultrasound-delivery interval influences the detection rate of LGA newborns. ***Methods:*** This was a retrospective cohort study of 9,585 singleton pregnancies. Maternal clinical characteristics, fetal ultrasound data obtained at 35 weeks, and pregnancy and perinatal outcomes were used to calculate EPWs to predict LGAs at delivery according to the customized and the non-customized (NC) Miguel Servet University Hospital (MSUH), the customized Figueras, the NC Fetal Medicine Foundation (FMF), the NC INTERGROWTH-21st, and the NC World Health Organization (WHO) standards. ***Results:*** For a 10% false-positive rate, detection rates for total LGAs at delivery ranged from 31.2% with the WHO (area under the curve [AUC] 0.77; 95% confidence interval [CI], 0.76–0.79) to 56.5% with the FMF standard (AUC 0.85; 95% CI, 0.84–0.86). Detection rates and values of AUCs to predict LGAs by ultrasound-delivery interval (range 1–6 weeks) show higher detection rates as the interval decreases. APO detection rates ranged from 2.5% with the WHO to 12.6% with the Figueras standard. ***Conclusion:*** The predictive ability of ultrasound estimated fetal weight at 35 weeks to detect LGA infants is significantly greater for FMF and MSUH NC standards. In contrast, the APO detection rate is significantly greater for customized standards. The shorter ultrasound-delivery interval relates to better prediction rates.

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Introduction

Screening for fetal growth abnormalities is an essential component of antenatal care, and fetal ultrasound plays a key role in this issue. Greater perinatal morbidity has been observed in large for gestational age (LGA) newborns [1] and stillbirth [2]. ISUOG Practice Guidelines for ultrasound assessment of fetal growth consider LGA fetuses as those with an estimated fetal weight (EFW) above the 90th centile, although the 95th centile, 97th centile, +2 standard deviations, and *Z*-score deviation have also been referred as cutoffs in the literature [3]. A randomized controlled trial published in 2015 showed that labor induction may decrease perinatal morbidity in newborns weighing more than 4,000 g or above the 95th percentile [4], thus the clinical interest in the early detection of LGAs. In addition, as has been suggested, universal versus selective LGA screening in the 3rd trimester improves the detection rate at delivery [5].

Since ultrasound assessment allows professionals to monitor intrauterine growth, different fetal growth standards have been based on the EFW to calculate the estimated percentile weight (EPW) using Hadlock et al.'s [6, 7] methodology or more recent studies that apply multilevel models. Although studies such as the one conducted by Gardosi et al. [8] have claimed that these standards can also be customized to maternal and fetal physiological variables, other studies have questioned the validity of customized standards [9, 10]. Moreover, international population standards have recently been published by EFW [11], including those from the INTERGROWTH-21st project [12, 13] and the World Health Organization (WHO) [14].

In order to provide new knowledge on the performance of growth standards, the main objective of this study was to compare 6 growth standards, customized and non-customized (NC), local and international ones, to detect LGA in term newborns by ultrasound at 35 weeks. With the same purpose, the secondary objective was to determine the predictive ability to detect adverse perinatal outcomes (APOs) and whether the ultrasound-delivery interval influences the detection rate of LGA newborns.

Methods

Study Design

This was a retrospective cohort study of births assisted at the Miguel Servet University Hospital (MSUH) between March 2012 and December 2016. The inclusion criteria were as follows: (1) live singleton pregnancies controlled in MSUH from the 1st trimester of gestation, (2) fetal ultrasound assessment at a gestational age of 35 (range 34–36) weeks, and (3) deliveries between 37 and 42 weeks of gestational age with fetuses without stillbirth associated with malformations or chromosomal abnormalities. From the 19,310 consecutive deliveries assisted in our hospital in the period studied, the 9,585 cases which fulfilled the specific inclusion criteria such as data availability to estimate percentile weights by standards were considered for the analysis. Selection of study participants is detailed in Figure 1. Our research was approved by the Clinical Research Ethics Committee of Aragon (PI20/414).

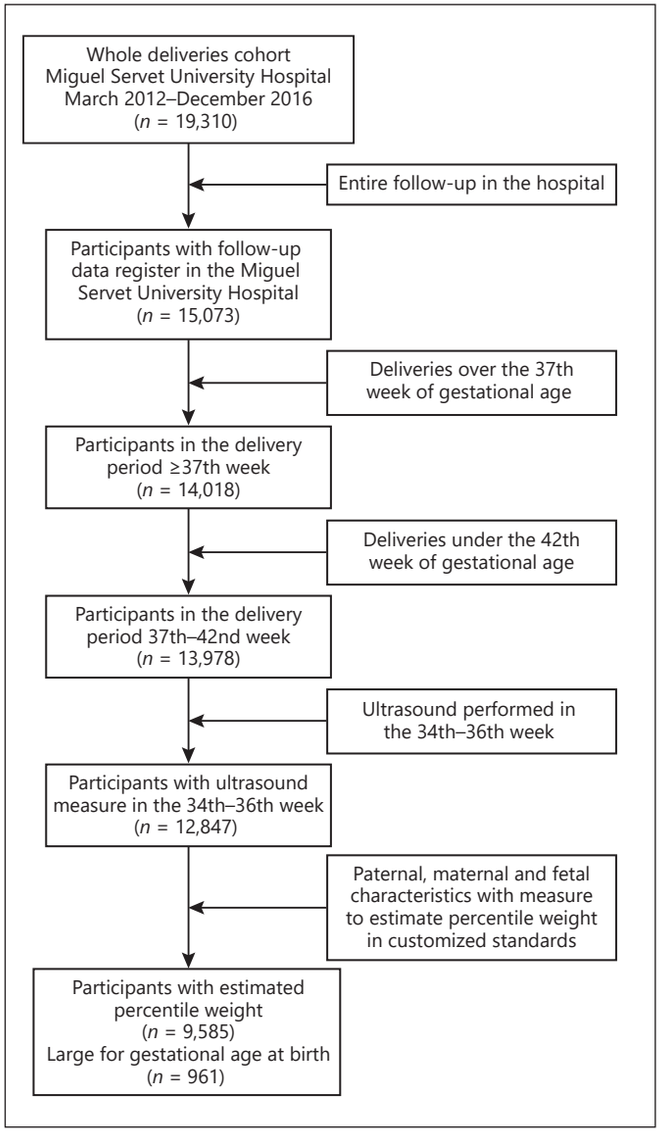

Fig. 1. Flowchart of patient recruitment.

The last menstrual period was adjusted by means of 1st trimester ultrasound results [15]. Universal ultrasound screening was performed at 35 weeks (range 34–36 weeks) at the Ultrasound and Prenatal Diagnosis Unit using either Voluson 730 Expert, E6, E8 (General Electric Healthcare, Zipf, Austria) or Aloka ProSound

Table 1. Parental baseline characteristics (top), and pregnancy (middle) and perinatal characteristics (bottom) of pregnancies

Clinical characteristic	Pregnancies (n = 9,585)
Parental characteristic	
Maternal age, years	33.3 (30.1–36.1)
Maternal BMI, kg/m^2	23.2 (21.1–26.2)
Maternal height, cm	163 (159–168)
Paternal height, cm	176 (172–181)
Parity	
0	5,077 (53.0%)
1	3,724 (38.9%)
≥2	784 (8.1%)
Maternal ethnicity	
Caucasian	9,243 (96.4%)
Asian	110 (1.1%)
African	232 (2.4%)
Maternal smoking habits	
Yes	1,546 (16.1%)
No	8,039 (83.9%)
Ultrasound parameters at 35 (34–36) weeks	
Gestational age (weeks) at ultrasound	35.1 (35.0–35.3)
EFW, g by Hadlock	2,495 (2,314–2,697)
EFW, g by Stirnemann	2,421 (2,209–2,648)
Percentile by standard	P50 (P10–P90)
NC MSUH	52.6 (11.9–93.3)
Customized MSUH	52.9 (12.2–92.9)
Figueras	59.3 (18.1–93.5)
INTERGROWTH-21st	51.9 (12.7–89.8)
WHO	43.1 (7.5–74.9)
FMF	37.6 (2.7–89.9)
Pregnancy and perinatal outcomes	
Gestational age at delivery, weeks	40.0 (39.1–40.7)
Newborn gender	
Female	4,652 (48.5%)
Male	4,933 (51.5%)
Birth weight, g	3,310 (3,030–3,590)
LGA	961 (10.02%)

Data are reported as n (%) or median (interquartile range). MSUH, Miguel Servet University Hospital; WHO, World Health Organization; NC, non-customized; FMF, Fetal Medicine Foundation; EFW, estimated fetal weight.

SSD-5000 (Hitachi Aloka Medical Systems, Tokyo, Japan) ultrasound machines. EFW was calculated with the formula of each model developed using the formula of Hadlock et al. [7] with biparietal diameter, cephalic and abdominal circumference, and femur length for the MSHU, Figueras et al. [16], WHO standards; cephalic and abdominal circumference, and femur length for the Fetal Medicine Foundation (FMF) standard. In addition, for the same reason, Stirnemann et al.'s [12] formula, which considers only cephalic and abdominal circumference, was used to estimate percentile weight for INTERGROWTH-21st.

The variables included in the study were maternal age and BMI at the beginning of pregnancy, parity, maternal and paternal height, maternal ethnic origin, smoking habits, infant gender, birth weight, and ultrasound EFW. We also collected perinatal outcomes to analyze APOs in LGAs at delivery, defined as the occurrence of 5-min Apgar score <7, instrumental or cesarean delivery for non-reassuring fetal status (NRFS), arterial cord blood pH < 7.10, and stillbirth.

Estimated Percentile Weight

EPWs were calculated according to 6 different customized and NC growth standards including population, population-customized, and international references. For the customized charts, Hadlock et al.'s [6] and Gardosi et al.'s [8] methodologies were used to develop (1) the MSUH standard customized for parity, age, BMI and maternal height, paternal height, and fetal gender, built using a modified version of Hadlock et al. [6, 7] growth charts adjusted to our population with a coefficient of variation that changes with gestational age (Savirón-Cornudella et al. [17]); (2) and the Barcelona Clinic Hospital (Figueras et al. [16]). For the NC standards,

Table 2. Diagnosis of APOs

	5-min Apgar score <7	Instrumental delivery for NRFS	Cesarean delivery for NRFS	Arterial cord blood pH <7.10	Stillbirth	Any APO
Total cohort	42	161	265	254	19	645
LGA, *n* (%)	1 (2.4)	13 (8.1)	17 (6.4)	16 (6.3)	1 (5.3)	44 (9.5)
EPW > 90, n *(%)*						
NC MSUH	4 (9.5)	11 (6.8)	33 (12.5)	25 (9.8)	3 (15.8)	67 (10.4)
Customized MSUH	4 (9.5)	16 (9.9)	37 (14.0)	30 (11.8)	3 (15.8)	79 (12.2)
Figueras	5 (11.9)	16 (9.9)	36 (13.6)	34 (13.4)	4 (21.1)	81 (12.6)
INTERGROWTH-21st	3 (7.1)	8 (5.0)	25 (9.4)	17 (6.7)	2 (10.5)	50 (7.8)
WHO	0 (0)	6 (3.7)	6 (2.3)	4 (1.6)	0 (0)	16 (2.5)
FMF	3 (7.1)	9 (5.6)	27 (10.2)	17 (6.7)	2 (10.5)	52 (8.1)

APOs, adverse perinatal outcomes; NC, non-customized; MSUH, Miguel Servet University Hospital; FMF, Fetal Medicine Foundation; NRFS, non-reassuring fetal status.

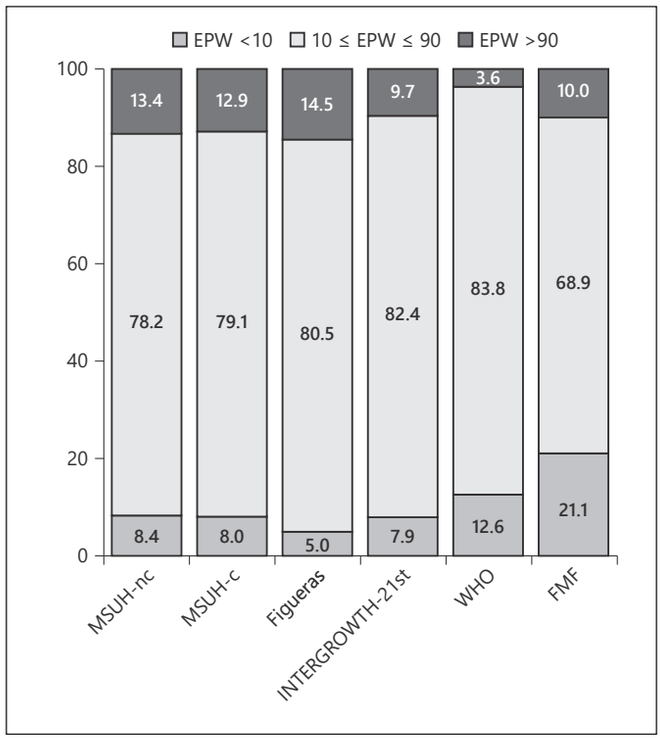

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Fig. 2. Bar diagram of percentages of small for gestational age (Orange), adequate for gestational age (Green), and LGA (Purple) provided by standards at 3rd trimester ultrasound (range 34–36 weeks). FMF, Fetal Medicine Foundation; MSUH, Miguel Servet University Hospital; WHO, World Health Organization; LGA, large for gestational age; EPW, estimated percentile weight.

we used (iii) a NC version of the MSUH standard (Savirón-Cornudella et al. [17]); (4) the international population INTERGROWTH-21st [12, 13], a multilevel mixed model which includes pregnant women without any pathology; (5) the international WHO fetal growth standard [14]; and (6) the FMF local growth multilevel mixed model (Nicolaides et al. [18]).

To assess ultrasound weight measures in the 3rd trimester, EPWs were estimated between 34 and 36 weeks of gestational age. The WHO EPW was calculated by interpolation of 5, 10, 25, 50, 75, 90, and 95 percentiles. As a gold standard for the analysis, LGA was defined as percentile birth weight over 90, using a growth reference for the Spanish population based on 9,362 birth weights [19].

Statistical Analysis

Once the data had been extracted, a descriptive table with the variables by ultrasound and at delivery was created. The predictive ability of EPW provided by the 6 standards used to predict LGAs was analyzed using the area under the receiver-operating characteristic curve (AUC) [20]. Sensitivity (detection rate) was established for false-positive rates (FPRs) of 5, 10, 15, and 20%. The percentile threshold point corresponding to the FPR values was also calculated. AUCs were compared using the DeLong test and sensitivities through a proportion comparison test. In addition, a sub-analysis was performed using a logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for an increase in 1% of the EPW at 35 weeks as a predictor for LGAs at delivery, performing a subclassification for different ultrasound-delivery intervals (1–6 weeks).

We analyzed the diagnostic ability of the standards using EPW > 90, and LGA birth weights to detect APOs: 5-min Apgar score <7, instrumental delivery for NRFS, cesarean delivery for NRFS, arterial cord blood pH < 7.10, and stillbirth. Comparison between APOs predicted by standards was performed using a proportion test. The analyses were performed using R version 3.6.1 language programming (R Foundation for Statistical Computing, Vienna, Austria) [21].

Results

Descriptive Results

Table 1 shows the descriptive characteristics of the subjects and displays medians and interquartile ranges

Table 3. Area under the receiver-operating characteristic curve and sensitivity analyses to detect LGA newborns, using EPW by ultrasound at 35 weeks (range 34–36 weeks) for different FPR percentages

Standard	AUC (95% CI)	Sensitivity (95% CI) and threshold percentile points[a]			
		FPR 5%	FPR 10%	FPR 15%	FPR 20%
NC MSUH	0.83 (0.82–0.85)	42.5 (39.3–45.7) (Thr 94.2)	55.8 (52.6–58.9) (Thr 88.6)	66.8 (63.7–69.8) (Thr 83.6)	73.8 (70.8–76.5) (Thr 78.3)
Customized MSUH	0.80 (0.78–0.81)	30.0 (27.1–33.0) (Thr 95.0)	45.3 (42.1.48.5) (Thr 89.5)	55.2 (51.9–58.3) (Thr 84.3)	62.7 (59.6–65.8) (Thr 79.2)
Figueras	0.81 (0.79–0.82)	32.3 (29.3–35.3) (Thr 95.4)	48.4 (45.2–51.6) (Thr 90.5)	58.4 (55.2–61.5) (Thr 86.1)	64.4 (61.3–67.4) (Thr 81.8)
INTERGROWTH-21st	0.84 (0.82–0.85)	36.3 (33.3–39.5) (Thr 91.5)	51.0 (47.8–54.2) (Thr 85.9)	62.0 (58.9–65.1) (Thr 80.1)	72.1 (69.1–74.9) (Thr 75.3)
WHO	0.77 (0.76–0.79)	25.9 (23.2–28.8) (Thr 81.9)	31.2 (28.3–34.3) (Thr 74.5)	35.3 (32.3–38.4) (Thr 73.7)	41.7 (38.6–44.9) (Thr 72.5)
FMF	0.85 (0.84-0-86)	38.2 (35.1–41.4) (Thr 92.2)	56.5 (53.3–59.7) (Thr 84.2)	65.7 (62.5–68.6) (Thr 76.9)	72.8 (69.9–75.6) (Thr 69.8)

MSUH, Miguel Servet University Hospital; Pc, percentile; WHO, World Health Organization; LGA, large for gestational age; NC, non-customized; FMF, Fetal Medicine Foundation; AUC, area under the curve; FPR, false-positive rate; CI, confidence interval; EPW, estimated percentile weight. [a] Sensitive threshold percentile: point that corresponds to a FPR value.

Table 4. Results of *p* value tests to compare standards: AUC and sensitivities (specificity 90%) to predict LGA, and percentage of APO diagnosis

	Customized MSUH			Figueras			INTERGROWTH-21st			WHO			FMF		
	AUC	sens	APOs	AUC	sens	APOs	AUC	sens	APOs	AUC	sens	APOs	AUC	sens	APOs
NC MSUH	<0.001	<0.001	0.334	<0.001	0.001	0.256	<0.001	0.039	0.121	<0.001	<0.001	<0.001	0.057	0.792	0.178
Customized MSUH				0.002	0.188	0.933	<0.001	0.014	0.009	<0.001	<0.001	<0.001	<0.001	<0.001	0.017
Figueras							<0.001	0.274	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	0.010
INTERGROWTH-21st										<0.001	<0.001	<0.001	<0.001	0.018	0.918
WHO													<0.001	<0.001	<0.001

NC, non-customized; MSUH, Miguel Servet University Hospital; FMF, Fetal Medicine Foundation; WHO, World Health Organization; APO, adverse perinatal outcome; AUC, area under the curve.

among groups for the 6 studied standards for EFWs by ultrasound at 35 weeks (range from 34 + 0 to 36 + 6 weeks) and weights at delivery and EPWs. Both WHO and FMF standards show an underestimation of the expected value by ultrasound (median values 43.1%, interquartile range 7.5–74.9, and 37.6%, interquartile range 2.7–89.9, respectively), and similarly, the Figueras standard shows an overestimation by ultrasound (median values 59.3%, interquartile range 18.1–93.5). EPW distributions are detailed in Figure 2, where a comparison of bar diagrams is shown for each standard. The rate of LGA at birth was 10.0% (n = 961). Regarding APOs, Table 2 shows that LGA deliveries include 9.5% (n = 44) APOs, 2.4% (n = 1) 5-min Apgar score <7, 8.1% (n = 13) instrumental deliveries for NRFS, 6.4% (n = 17) cesarean deliveries for NRFS, 6.3% (n = 16) neonatal acidemia (pH cord blood pH < 7.10), and 5.3% (n = 1) stillbirth.

Comparison of Growth Standards

Table 3 displays values of AUCs and sensitivities plus the percentile threshold point for different FPRs to predict LGAs at delivery by ultrasound. For a 10% FPR, the detection rates for LGAs for all the standards ranged be-

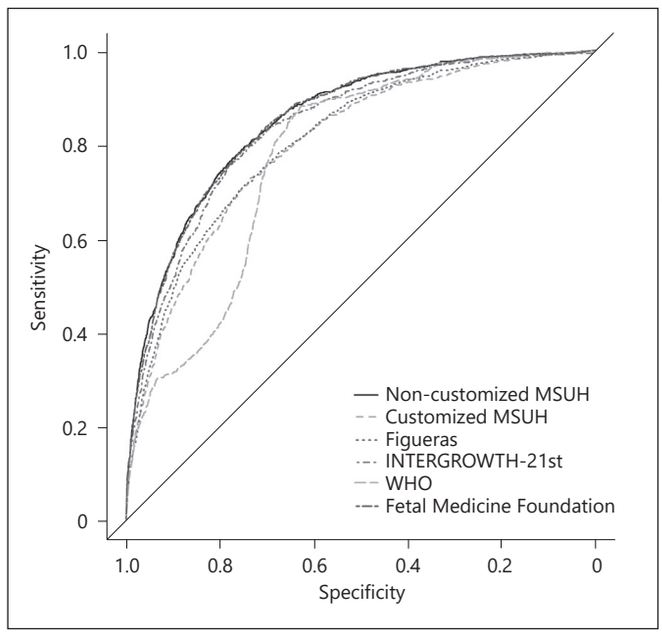

Fig. 3. Receiver-operating characteristic curves: comparison of fetal growth standards for prediction of LGA newborns using EPW by ultrasound at 35 weeks. MSUH, Miguel Servet University Hospital; WHO, World Health Organization.

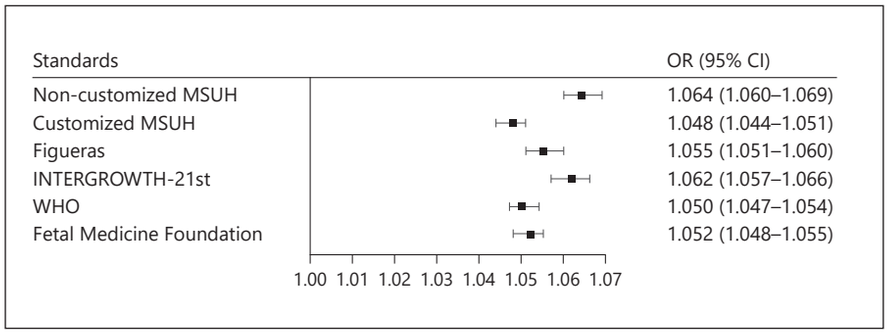

Fig. 4. ORs and 95% CIs of standards in order to predict LGA newborns according to EPW by ultrasound at 35 weeks. MSUH, Miguel Servet University Hospital; WHO, World Health Organization; ORs, odds ratios; CIs, confidence intervals.

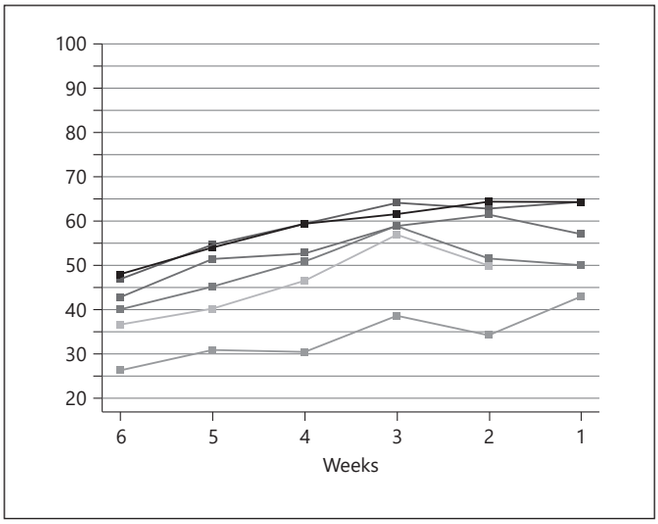

Fig. 5. Prediction of LGA cases by standards by ultrasound-delivery interval (1–6 weeks) for a 10% FPR. Growth standards: NC MSUH [17] (dark blue line), customized MSUH [17] (green line), Figueras et al. [16] (red line), INTERGROWTH-21st [13] (purple line), WHO [14] (orange line), and FMF [18] (dark slate grey line). LGA, large for gestational age; NC, non-customized; MSUH, Miguel Servet University Hospital; WHO, World Health Organization; FMF, Fetal Medicine Foundation; FPR, false-positive rate.

tween 31.2% with the WHO standard (AUC 0.77; 95% CI, 0.76–0,79) and 56.5% with the FMF standard (AUC 0.85; 95% CI, 0.84–0.86). These values were obtained with percentile threshold points over 88.6, 89.5, 90.5, 85.9, 74.5, and 84.2% for, respectively, NC and customized MSUH, Figueras, INTERGROWTH-21st, WHO, and FMF standards. For a 20% FPR, the detection rates ranged from 41.7 to 73.8%, using 78.3, 79.2, 81.8, 75.3, 72.5%, and 69.8% as the percentile threshold points.

Figure 3 illustrates the receiver-operating characteristic curve comparison and the AUC for the prediction of LGAs at delivery by ultrasound at 35 weeks. Figure 4 displays the results of the logistic regression model with the ORs and 95% CIs to predict LGAs by ultrasound at 35 weeks according to the standards. Online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000510020) shows the concordance between predicted LGAs at delivery by standards using EPW > 90.

p Values of the comparisons of the standard AUC values and sensitivity for a 90% specificity are shown in Table 4. The FMF and the NC MSUH standards showed no statistically significant differences between them, but with greater LGA prediction ability than INTERGROWTH-21st, Figueras, and WHO standards. Besides, in the comparison, INTERGROWTH-21st showed significant differences from customized MSHU and WHO standards, but not with the Figueras standard. Finally, customized standards did not show differences between them, but with greater LGA prediction ability than the WHO standard.

Regarding APO prediction by EPW > 90, in Table 2 we show that the customized Figueras and the MSUH standards reached the greatest detection rate, 12.6 and 12.2%, respectively. No statistically significant difference was detected with the NC MSUH (10.4%), although the differences with the FMF (8.1%), INTERGROWTH-21st (7.8%), and WHO (2.5%) standards were significant. The instrumental deliveries for NRFS, cesarean deliveries for NRFS, and neonatal acidemia APOs might explain those differences. *p* values of all comparisons are illustrated in Table 4.

Comparison of Growth Standards by Ultrasound-Delivery Interval

Online suppl. Table 2 displays values of AUCs and sensitivities for different FPRs to predict LGAs by ultrasound-delivery interval (range 1–6 weeks). Figure 5 shows the prediction of LGA cases by standard by ultrasound-delivery interval (1–6 weeks) for a 10% FPR. The ob-

served results show higher detection rates as the interval decreases. Online suppl. Figure 1 illustrates the receiver-operating characteristic curve comparison of fetal growth standards for the prediction of LGA newborns according to the ultrasound-delivery interval (range 1–6 weeks). Online suppl. Figure 1 displays ORs and 95% CIs of standards in order to predict LGAs by ultrasound-delivery interval (range 1–6 weeks).

Discussion

Principal Findings

Our study has demonstrated the utility of EPW by ultrasound exam at 35 weeks (range 34 + 0 to 36 + 6 weeks) as a predictor of LGAs at delivery at term with any model studied. The comparison of 6 growth standards showed similar good predictive ability for LGAs, and with the exception of the WHO standard, NC standards present a greater predictive ability to detect LGAs at delivery. The NC MSHU and FMF standards fit better to a 10% detection of LGAs at delivery and with an ultrasound-delivery interval of 1 week; therefore, MSHU and FMF standards have a higher detection rate. On the contrary, when we analyzed LGAs with the APO predictive ability of the 6 standards by percentile weight >90 at the 35th week of gestational age, customized Figueras and MSUH standards showed the greatest diagnostic ability, with statistically significant differences with 3 of the 4 NC models. A previous study did not find any significant difference between customized and NC standards analyzing the predictive ability of EPW to detect APOs; by contrast, using EPW >90, we detected significant differences [9]. The shorter ultrasound-delivery interval is related to better prediction rates with all the standards.

The predictive capacity for LGAs at delivery was not perfect for the 6 growth standards however, and several studies of ultrasound accuracy have consistently reported an EFW underestimation in LGAs due to the intrinsic error of ultrasound [22], which could, at least partially, justify these detection rates. Lowering the percentile threshold point by ultrasound would, in our view, improve the detection of LGAs at delivery but would increase FPRs. In any case, unless the birth is scheduled, it will be difficult to identify the best time to perform the ultrasound.

Prediction of LGAs at Delivery by Ultrasound

Sovio et al. [5] in 2018 supported universal 36-week ultrasound versus selective scans to screen for LGA infants, with an improvement in detection rates from 27% (FPR 1.7% and AUC 0.71) to 38% (FPR 3.2% and AUC 0.87). Their study included preterm deliveries and a low rate of LGAs of 4.6%, which could explain the lower FPR in their study.

In 2012, Zhang et al. [23] showed a higher predictive ability for LGA infants when an ultrasound was performed close to delivery (AUC 0.843 at 33 weeks and AUC 0.889 at 37 weeks). Souka et al.'s [24] 2013 study reported a 53% detection rate (FPR 10% and AUC 0.85) by ultrasound at 32–33 weeks, which increased to 63% (FPR 10% and AUC 0.87) by ultrasound at 35–36 weeks. Their study matched our results, although it is based on different inclusion criteria (LGA infants defined as higher than the 95 percentile). This is probably because the fetus has less time to modify its weight percentile until birth as the ultrasound-delivery interval decreases.

In a similar line, a longitudinal cohort study by Tarca et al. [25], carried out in 2016, displayed a detection rate of 54% of LGA infants (FPR 10% and AUC 0.84). A possible reason for their lower detection rates might be associated to the earlier ultrasound at 34 weeks. Frick et al. [26] also published similar results scanning at 30–34 weeks with a 41.3% detection rate (FPR 10% and AUC 0.760), which increased to 48.6% at 35–37 weeks (FPR 10% and AUC 0.803). Their work considered maternal factors and also emphasized that the ability to predict increases in LGA infants when estimation of weight assessment was performed closer to delivery.

We could argue that the cutoff point of the 90th percentile by ultrasound seems to be limited to the prediction of LGAs at delivery. Screening by maternal factors and biomarkers in the 3 trimesters of pregnancy has been developed for LGA neonates similar to SGA standards, but with limited results [25]. Understandably, further studies should be conducted which can improve the detection rate of LGAs.

Strengths and Limitations of the Study

As one of the strengths of our research, we should highlight the large sample size of the data analyzed, approximately 10,000 pregnancies. It is also noteworthy that our statistical approach and comparison present a low risk of bias. However, among the limitations of our research, we should mention the fact that our study is restricted to 1 population with a high proportion of Caucasians (96.4%), and our results might therefore show a risk of bias due to the retrospective nature of the study. Hence, future studies might benefit from a more detailed prospective protocol.

Clinical Relevance

The predictive ability of ultrasound EFW at 35 weeks for LGA infants is similarly good for the 6 growth standards, despite the significant improvement detected in the use of NC local or international standards with no statistically significant differences between them. In contrast, when focusing on the use of EPW > 90 at week 35 for the prediction of LGAs with APOs, customized standards demonstrated an advantage over NC standards. We would thus conclude that standards with a shorter ultrasound-delivery interval would be related to better prediction rates.

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Statement of Ethics

The research presented in the manuscript was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies, and was approved by the research institute's committee on human research (Clinical Research Ethics Committee of Aragon PI20/414). No patient consents were required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.S.C., L.M.E., and R.A.G. contributed to the conception of the study. R.S.C., L.M.E., F.R.P.L., B.C.L., and M.T.D. contributed to the design of the work. P.D.P. and M.T.D. carried out data acquisition. L.M.E., R.A.G., and G.S. performed statistical analyses. All authors were involved in the interpretation of the study results, and the drafting and revision of the manuscript, and all approved the final version to be published.

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Article

Prediction of Late-Onset Small for Gestational Age and Fetal Growth Restriction by Fetal Biometry at 35 Weeks and Impact of Ultrasound–Delivery Interval: Comparison of Six Fetal Growth Standards

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Abstract: Small-for-gestational-age (SGA) infants have been associated with increased risk of adverse perinatal outcomes (APOs). In this work, we assess the predictive ability of the ultrasound-estimated percentile weight (EPW) at 35 weeks of gestational age to predict late-onset SGA and APOs, according to six growth standards, and whether the ultrasound–delivery interval influences the detection rate. To this purpose, we analyze a retrospective cohort study of 9585 singleton pregnancies. EPWs at 35 weeks were calculated to the customized Miguel Servet University Hospital (MSUH) and Figueras standards and the non-customized MSUH, Fetal Medicine Foundation (FMF), INTERGROWTH-21st, and WHO standards. As results of our analysis, for a 10% false positive rate, the detection rates for SGA ranged between 48.9% with the customized Figueras standard (AUC 0.82) and 60.8% with the non-customized FMF standard (AUC 0.87). Detection rates to predict SGA by ultrasound–delivery interval (1–6 weeks) show higher detection rates as intervals decrease. APOs detection rates ranged from 27.0% with FMF to 7.9% with the Figueras standard. In conclusion, the ability of EPW to predict SGA at 35 weeks is good for all standards, and slightly better for non-customized standards. The APO detection rate is significantly greater for non-customized standards.

Keywords: adverse perinatal outcomes; birth weight; estimated fetal weight; estimated percentile weight; fetal growth standard; small for gestational age; ultrasound

1. Introduction

Screenings for fetal growth abnormalities are essential components of antenatal care, and fetal ultrasound plays a key role in the assessment of these conditions [1–3]. Small-for-gestational-age (SGA) infants—those with a birth weight below the 10th percentile

according to the standards [4]—have been associated with increased risk of adverse perinatal outcomes (APOs) [5].

These fetuses are the leading cause of stillbirth [6–8], and have more risks of both neonatal morbidity [9] and mortality [10,11]. Recent studies have shown that an early diagnosis of SGA in the third trimester can help to reduce APOs, reflecting the benefit of prenatal diagnosis in these cases [12,13], although the time to perform the ultrasound is not clearly established.

Several studies customized or not to maternal and fetal physiological variables have been proposed to predict SGA [14]; these fetal growth standards [15–17] are based on Hadlock et al.'s methodology [18,19], or on new multilevel models [20–22], and can be customized to maternal and fetal physiological variables [23]. The estimation of the percentile adjusted for maternal and fetal characteristics is the property that postulates customized standards as better detectors of adverse perinatal outcomes than population-based standards (non-customized (NC)) [24]. The Royal College of Obstetricians and Gynecologists (RCOG) [25] recommends the use of customized birthweight curves to identify SGA fetuses; the adjustment of fetal weight should be performed individually, and not by population—although some studies have questioned the superiority of the EPW by customized standards and its association with APOs [26,27], and SGA with APOs [28].

Furthermore, new standards have recently been published by EFW [29], including international standards from the World Health Organization (WHO) [17] and the INTERGROWTH-21st project [20,21], and local standards from the Fetal Medicine Foundation (FMF) [22]. According to the recent review by McCowan et al. (2018), international population ultrasound standards still require more comparative studies for validation [5].

Since the controversy arose about the most appropriate method to predict SGA, and the lack of comparative assessment for the cited approaches, the objective of this study is to compare the ability of EPW—according to six growth standards, by ultrasound at 35 weeks, including population, population-customized, and international references—to predict late-onset SGA, defined as a birth weight below the 10th percentile at term delivery. The secondary objective is to determine whether the ultrasound–delivery interval influences the detection rate of SGA newborns.

2. Materials and Methods

2.1. Study Design

This was a retrospective cohort study of births assisted at the Miguel Servet University Hospital (MSUH), between March 2012 and December 2016. The inclusion criteria were as follows: live singleton pregnancies controlled in MSUH from the first trimester of gestation; fetal ultrasound assessment at gestational age of 35 (range 34–36) weeks; and deliveries between 37 and 42 weeks of gestational age of fetuses without stillbirth associated with malformations or chromosomal abnormalities. Of the 19,310 consecutive deliveries assisted in our hospital in the period studied, the 9585 cases that fulfilled the specific inclusion criteria—such as data availability to estimate percentile weights by standards—were considered for the analysis. Study participants' selection samples are detailed in Figure 1.

The last menstrual period was adjusted by first trimester ultrasound [30]. Universal ultrasound screening was performed at 35 weeks (range 34–36 weeks) at the Ultrasound and Prenatal Diagnosis Unit using either a Voluson 730 Expert, E6, E8 ultrasound machine (General Electric, Healthcare, Zipf, Austria) or an Aloka Prosound SSD-5000 (Hitachi Aloka Medical Systems, Tokyo, Japan). This ultrasound corresponds to the one that is routinely performed in all pregnancies at our center to try to increase the detection of fetal growth alterations [5].

EFW was calculated with the formula of each standard to which it was built. We used Hadlock et al.'s [19] formula, which combines biparietal diameter, cephalic and abdominal circumference, and femur length, for the MSHU, Figueras et al., and WHO standards; and the version that uses cephalic and abdominal circumference and femur length for the Fetal Medicine Foundation (FMF) standard. In addition, Stirnemann et al.'s formula [20],

including only cephalic and abdominal circumference, was used to estimate percentile weight for the INTERGROWTH-21st standard.

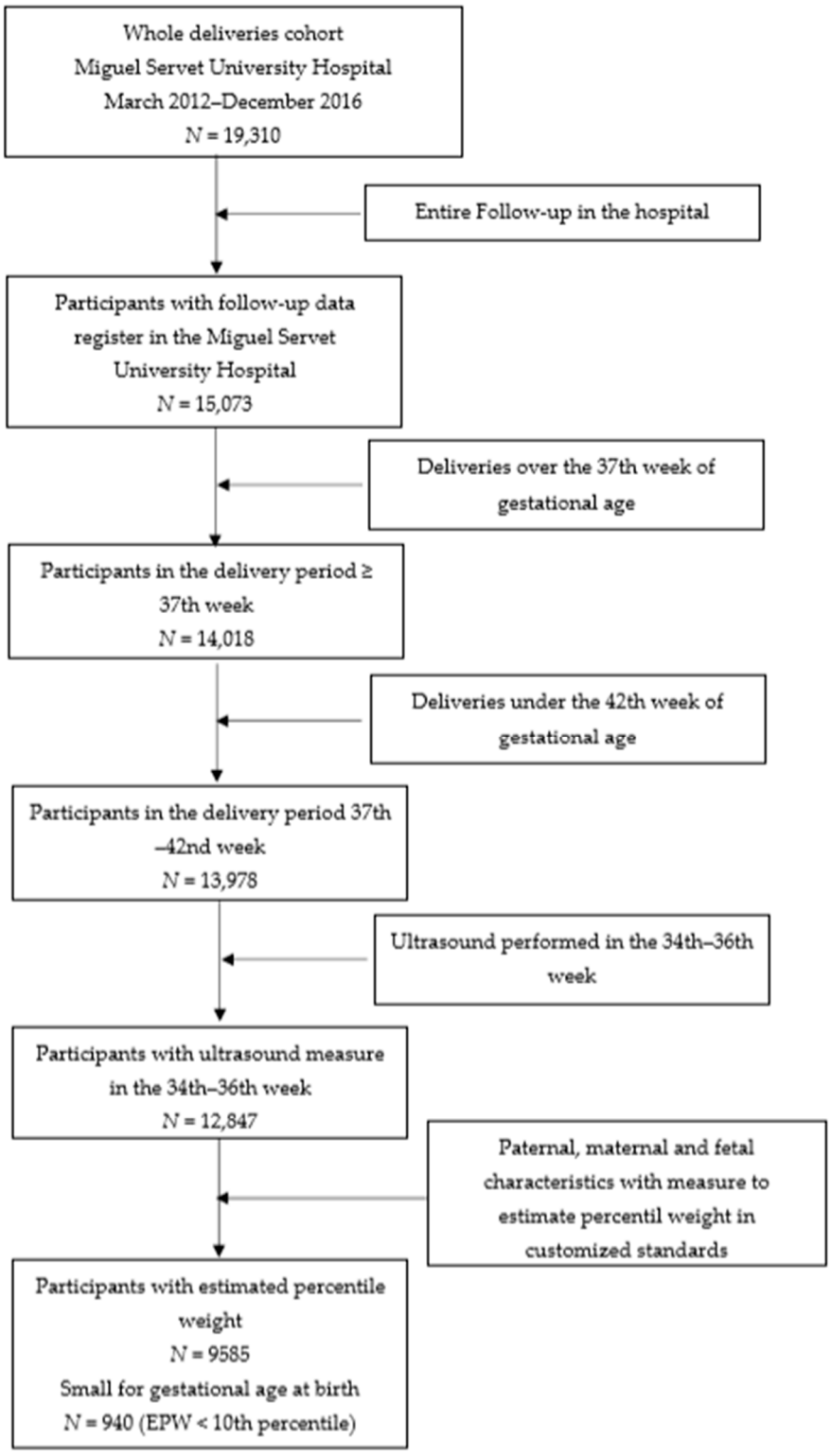

Figure 1. Flowchart of patient recruitment; EPW: estimated percentile weight.

For the calculation of the EPW, we collected in the study the maternal age and body mass index (BMI) at the beginning of pregnancy, parity, maternal and paternal height, maternal ethnic origin, smoking habits, infant gender, birth weight, and ultrasound EFW.

We also collected perinatal outcomes in order to analyze APOs in SGA infants at delivery, defined as the occurrence of a 5-min Apgar score < 7, instrumental or cesarean delivery for non-reassuring fetal status, arterial cord blood pH < 7.10, and stillbirth.

2.2. Estimated Percentile Weight

EPWs were calculated according to 6 different customized and NC growth standards, including population, population-customized, and international references. For the customized standards, the methodologies of Hadlock et al. [18] and Gardosi et al. [23] were used for (1) the MSUH standard customized for parity, age, BMI, maternal height, paternal height, and fetal gender, built using a modified version of Hadlock et al.'s growth charts adjusted to our population, with a coefficient of variation that changes with gestational age (Saviron-Cornudella et al. [16]); (2) and the Barcelona Clinic Hospital (Figueras et al. [15]). For the NC standards, we used (3) an NC version of the MSUH standard (Saviron-Cornudella et al. [16]); (4) the international population INTERGROWTH–21st [20,21]—a multilevel mixed model whose main characteristic is that it includes pregnant women without pathology; (5) the international WHO fetal growth standard [17], and (6) the FMF local growth multilevel mixed model (Nicolaides at al [22]).

To assess ultrasound weight measures in the third trimester, EPWs were estimated between 34 and 36 weeks of gestational age. The WHO EPW was calculated by interpolation of the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles.

As a gold standard for the analysis, SGA was defined as a birth weight below the 10th percentile, using a growth reference for the Spanish population based on 9362 birthweights [31]. We did not focus our analysis on intrauterine growth-restricted fetuses (IUGRs). As we did not perform Doppler ultrasound universally (only in cases of estimated fetal weight < 10th percentile), we did not study the subgroup of SGA fetuses at delivery with altered Doppler ultrasound. This is because a significant percentage of SGA fetuses at delivery did not present an estimated fetal weight <10th percentile by ultrasound.

2.3. Statistical Analysis

Data were descriptively analyzed using medians and interquartile ranges for continuous variables, and absolute and relative frequencies for categorical variables. The ability of EPW provided by the six standards to predict SGA was analyzed using the area under the receiver operating characteristic curve (AUC) [32]. Sensitivity (detection rate) was established for false positive rates (FPR) of 5, 10, 15, and 20%. The percentile threshold point corresponding to the FPR values was also calculated. AUCs were compared using the DeLong test, and sensitivities through a proportion comparison test.

In addition, we built logistic regression models to estimate the OR and 95% confidence interval that correspond to an increase of 1% in the EPW at 35 weeks, as a predictor for SGA at delivery, performing a subanalysis for different ultrasound–delivery intervals (1–6 weeks).

We analyzed the diagnostic ability of the EPW 10th percentile and SGA birthweights to detect the following adverse perinatal outcomes: 5-min Apgar score < 7, instrumental delivery for non-reassuring fetal status (NRFS), cesarean delivery for NRFS, arterial cord blood pH < 7.10, and stillbirth. Comparison between APOs predicted by standards was performed using a proportion test.

Analyses were performed using R version 3.6.2 language programming (The R Foundation for Statistical Computing, Vienna, Austria) [33].

3. Results

3.1. Descriptive Results

Table 1 shows the descriptive characteristics of the pregnant women, and also displays medians and percentiles 10 (P10) and 90 (P90) among groups for the six studied standards for EFWs by ultrasound at 35 weeks (range from 34+0 to 36+6 weeks). WHO and FMF standards show an underestimation of the median expected value (50%) by ultrasound (median

values 43.1%, P10–P90 range 7.5–74.9, and 37.6%, P10–P90 range 2.7–89.9, respectively), while the Figueras standard shows an overestimation by ultrasound (median values 59.3%, P10–P90 range 18.1–93.5).

Table 1. Parental baseline characteristics (top), pregnancy (middle), and perinatal characteristics (bottom) of pregnancies. Data are reported as n (%) or medians (interquartile range); MSUH: Miguel Servet University Hospital; NRFS: non-reassuring fetal status; WHO: World Health Organization.

Clinical Characteristics	Pregnancies (n = 9585)
Parental characteristics	
Maternal age (years)	33.3 (30.1–36.1)
Maternal body mass index (kg/m^2)	23.2 (21.1–26.2)
Maternal height (cm)	163 (159–168)
Paternal height (cm)	176 (172–181)
Parity	
0	5077 (53.0%)
1	3724 (38.9%)
$\geq$ 2	784 (8.1%)
Maternal ethnicity	
Caucasian	9243 (96.4%)
Asian	110 (1.1%)
African	232 (2.4%)
Maternal smoking habits	
Yes	1546 (16.1%)
No	8039 (83.9%)
Ultrasound parameters at 35 (34–36) weeks	
Gestational age (weeks) at ultrasound	35.1 (35.0–35.3)
Estimated fetal weight (grams) by Hadlock	2495 (2314–2697)
Estimated fetal weight (grams) by Stirnemann	2421 (2209–2648)
Percentile by standard	P50 (P10–P90)
Non-customized MSUH	52.6 (11.9–93.3)
Customized MSUH	52.9 (12.2–92.9)
Figueras	59.3 (18.1–93.5)
INTERGROWTH-21st	51.9 (12.7–89.8)
WHO	43.1 (7.5–74.9)
Fetal Medicine Foundation	37.6 (2.7–89.9)
Pregnancy and perinatal outcomes	
Gestational age at delivery	40.0 (39.1–40.7)
Newborn gender	
Female	4652 (48.5%)
Male	4933 (51.5%)
Birth weight	3310 (3030–3590)
Small for gestational age (<10th percentile)	902 (9.4%)
5-min Apgar score < 7	42 (0.4%)
Instrumental delivery for NRFS	161 (1.7%)
Cesarean delivery for NRFS	265 (2.8%)
Arterial cord blood pH < 7.10	254 (2.6%)
Stillbirth	19 (0.2%)
Any adverse perinatal outcome *	645 (6.7%)

* Excluding SGA.

EPW distributions are detailed in Figure 2, where a comparison of the percentage of SGA is shown for each standard. The rate of SGA at birth in our cohort was 9.4% (n = 902).

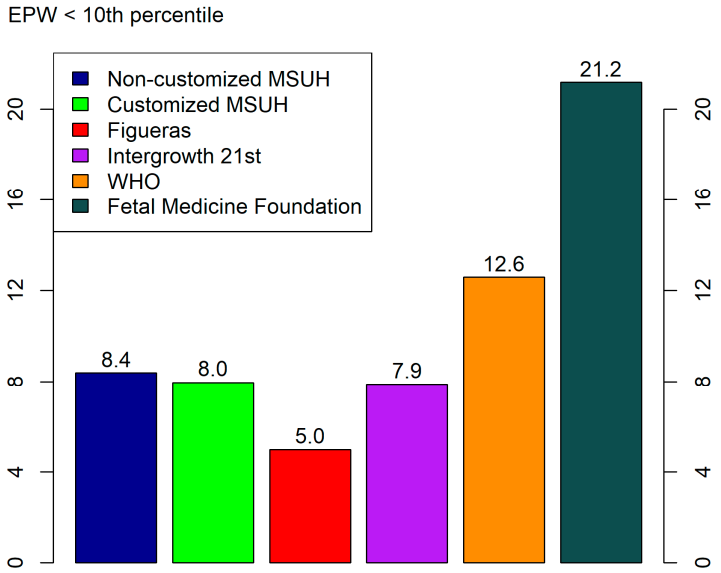

Figure 2. Percentage of small for gestational age (estimated percentile weight (EPW) <10th percentile) cases provided by standards at the third trimester (34th–36th week). Growth standards: non-customized Miguel Servet University Hospital (MSUH)16, customized MSUH, Figueras et al., INTERGROWTH-21st, World Health Organization (WHO), and Fetal Medicine Foundation.

Regarding APOs, Table 2 shows that SGA deliveries included 21.6% (n = 139) APOs, 28.6% (n = 12) 5-min Apgar scores < 7, 19.9% (n = 32) instrumental deliveries for NRFS, 26.8% (n = 71) cesarean deliveries for NRFS, 17.7% (n = 45) neonatal acidemia (pH cord blood pH < 7.10), and 26.3% (n = 5) stillbirth.

Table 2. Diagnosis of adverse perinatal outcomes (APOs); EPW: estimated percentile weight at 35 weeks (range 34–36 weeks); MSUH: Miguel Servet University Hospital; NRFS: non-reassuring fetal status; WHO: World Health Organization.

	5-Min Apgar Score < 7	Instrumental Delivery for NRFS	Cesarean Delivery for NRFS	Arterial Cord Blood pH < 7.10	Stillbirth	Any APO
Total cohort	42	161	265	254	19	645
SGA	12 (28.6%)	32 (19.9%)	71 (26.8%)	45 (17.7%)	5 (26.3%)	139 (21.6%)
EPW < 10						
Non-customized MSUH	8 (19.0%)	15 (9.3%)	43 (16.2%)	26 (10.2%)	5 (26.3%)	76 (11.8%)
Customized MSUH	6 (14.3%)	9 (5.6%)	38 (14.3%)	22 (8.7%)	5 (26.3%)	62 (9.6%)
Figueras	5 (11.9%)	8 (5.0%)	32 (12.1%)	18 (7.1%)	4 (21.1%)	51 (7.9%)
INTERGROWTH-21st	7 (16.7%)	11 (6.8%)	39 (14.7%)	26 (10.2%)	5 (26.3%)	69 (10.7%)
WHO	12 (28.6%)	24 (14.9%)	57 (21.5%)	42 (16.5%)	7 (36.8%)	112 (17.4%)
FMF	17 (40.5%)	37 (23.0%)	89 (33.6%)	62 (24.4%)	10 (52.6%)	174 (27.0%)

3.2. Comparison of Standards

Table 3 displays values of AUCs and sensitivities plus the percentile threshold points for different FPRs to predict SGA at delivery by ultrasound at 35 weeks (range 34+0–36+6 weeks). For a 10% FPR, the detection rates for SGA for all standards ranged between 48.9% with the Figueras standard (AUC: 0.82; 95% CI: 0.80–0.83) to 60.8% with the Fetal Medicine Foundation standard (AUC: 0.87; 95% CI: 0.85–0.88). These values were obtained with percentile threshold points below 17.3%, 16.3%, 22.9%, 17.3%, 11.1% and 5.3% for NC MSUH, customized MSUH, Figueras, INTERGROWTH-21st, WHO, and FMF standards, respectively. For a 20% FPR, the detection rates were between 66.4 and 78.92%,

using 28.5%, 28.1%, 34.6%, 28.1%, 19.1%, and 13.1% as percentile threshold points for the abovementioned standards, respectively.

Table 3. Area under the receiver operating characteristic curve and sensitivity analyses to detect small for gestational age cases by ultrasound at 35 weeks (range 34–36 weeks) for different false positive rate (FPR) percentages; MSUH: Miguel Servet University Hospital; Pc: percentile; WHO: World Health Organization. * Sensitive threshold percentile (Thr): percentile point that corresponds to a false positive rate value.

Prediction of Small for Gestational Age by Standard	Area under the Curve (95% C.I.)	Sensitivity (95% C.I.) and Threshold Percentile Points *			
		FPR 5%	FPR 10%	FPR 15%	FPR 20%
Small for gestational age					
Non-customized MSUH	0.87 (0.85–0.88)	42.6 (39.4–45.9) (Thr: 10.3)	60.4 (57.1–63.6) (Thr: 17.3)	70.5 (67.4–73.4) (Thr: 23.3)	78.2 (75.3–80.8) (Thr: 28.5)
Customized MSUH	0.82 (0.80–0.83)	35.5 (32.3–38.6) (Thr: 9.9)	51.1 (47.8–54.4) (Thr: 16.3)	60.9 (57.6–64.1) (Thr: 22.7)	67.6 (64.4–70.6) (Thr: 28.1)
Figueras	0.82 (0.80–0.83)	35.4 (32.3–38.6) (Thr: 14.5)	48.9 (45.6–52.2) (Thr: 22.9)	60.8 (57.5–64.0) (Thr: 29.5)	66.4 (63.2–69.5) (Thr: 34.6)
INTERGROWTH-21st	0.85 (0.84–0.86)	37.8 (34.6–41.1) (Thr: 10.2)	56.3 (53.0–59.6) (Thr: 17.3)	66.7 (63.5–69.8) (Thr: 22.9)	73.7 (70.7–76.5) (Thr: 28.3)
WHO	0.84 (0.83–0.85)	38.6 (35.4–41.9) (Thr: 6.2)	56.1 (52.8–59.4) (Thr: 11.1)	61.0 (57.7–64.2) (Thr: 14.6)	70.6 (67.5–73.5) (Thr: 19.1)
Fetal Medicine Foundation	0.87 (0.85–0.88)	42.4 (39.2–45.7) (Thr: 1.9)	60.8 (57.5–64.0) (Thr: 5.3)	70.7 (67.6–73.6) (Thr: 9.3)	76.3 (73.4–79.0) (Thr: 13.1)

Figure 3 illustrates the receiver operating characteristic curve comparison and AUC for the prediction of SGA at delivery by ultrasound at 35 weeks. Figure 4 displays the results of the logistic regression model with the ORs and 95% CIs to predict SGA by ultrasound at 35 weeks, according to the standards.

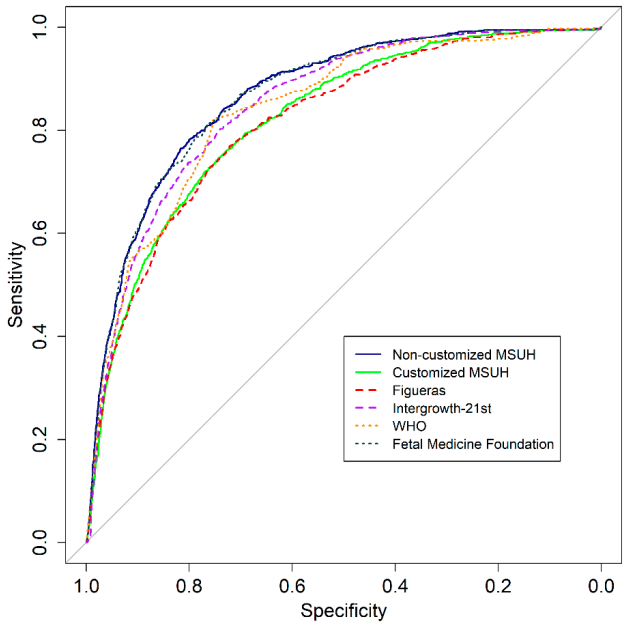

Figure 3. Receiver operating characteristic curves: comparison of fetal growth standards and area under the curve (95% CIs) for prediction of small for gestational age newborns, using estimated percentile weight by ultrasound at 35 weeks. Growth standards: non-customized Miguel Servet University Hospital (MSUH), customized MSUH, Figueras et al., INTERGROWTH-21st, World Health Organization (WHO), and Fetal Medicine Foundation.

p-values of the comparisons of the standard AUC values and sensitivity for a 90% specificity are shown in Table 4. The Fetal Medicine Foundation and the non-customized MSUH standards showed no statistically significant differences between them, with greater SGA prediction ability than the Intergrowth-21st, Figueras, and WHO standards. Moreover, in the comparison, the Intergrowth-21st and WHO standards showed significant differences from the customized MSHU and Figueras standards. Finally, customized standards did not show differences between them.

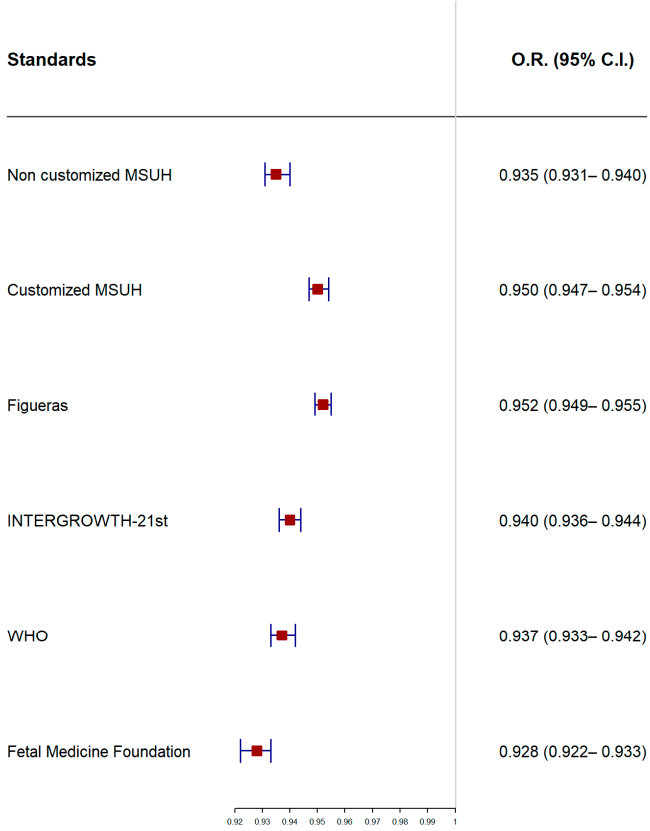

Figure 4. Odds ratios (ORs) and 95% confidence intervals (CIs) of standards in to predict small for gestational age according to estimated percentile weight by ultrasound at 35 weeks; MSUH: Miguel Servet University Hospital; WHO: World Health Organization.

Table 4. Results of *p*-value tests to compare standards: area under the receiver operating characteristic curve (AUC) and sensitivities (specificity 90%) to predict small for gestational age; and percentage of adverse perinatal outcome (APO) diagnosis; NC: non-customized; C: customized; MSUH: Miguel Servet University Hospital; WHO: World Health Organization.

	Customized MSUH			**Figueras**			**INTERGROWTH-21st**			**WHO**			**Fetal Medicine Foundation**		
	AUC	**Sens**	**APOs**	**AUC**	**Sens**	**APOs**	**AUC**	**Sens**	**APOs**	**AUC**	**Sens**	**APOs**	**AUC**	**Sens**	**APOs**
NC MSUH	<0.001	<0.001	0.242	<0.001	<0.001	0.025	<0.001	0.086	0.597	<0.001	0.071	0.006	0.169	0.900	<0.001
C MSUH				0.053	0.375	0.325	<0.001	0.030	0.580	<0.001	0.037	<0.001	<0.001	<0.001	<0.001
Figueras							<0.001	0.002	0.103	<0.001	0.003	<0.001	<0.001	<0.001	<0.001
IG-21st										0.094	0.970	<0.001	<0.001	0.058	<0.001
WHO													<0.001	0.048	<0.001

Regarding APO prediction by EPW < 10, in Table 2 we show that the Fetal Medicine Foundation and WHO standards reached the greatest detection rates—27.0% and 17.4% respectively—with statistically significant differences between them and the rest of standards. No statistically significant differences were detected in the any of the possible

comparisons between the non-customized MSUH (11.8%), INTERGROWTH-21st (10.7%), customized MSUH (9.6%), and Figueras (7.9%) standards, with the unique exception of the significant difference between the non-customized MSUH and Figueras standards. The instrumental deliveries for NRFS, cesarean deliveries for NRFS, and neonatal acidemia APOs might explain those differences. *p*-values of all comparisons are illustrated in Table 4.

3.3. Ultrasound-Delivery Interval: Comparison of Standards

Table 5 displays values of AUCs and sensitivities for different FPRs to predict SGA by ultrasound–delivery interval (range 1–6 weeks). The observed results show higher detection rates as the interval decreases. Figure 5 shows the prediction of small for gestational age cases, by standard, by ultrasound–delivery interval (1–6 weeks), for a 10% false positive rate.

Table 5. Area under the receiver operating characteristic curve and sensitivity analyses to predict small for gestational age newborns using estimated percentile weight by ultrasound at 35 weeks (range 34–36 weeks), for different false positive rate (FPR) percentages and ultrasound–delivery intervals (1–6 weeks); MSUH: Miguel Servet University Hospital; WHO: World Health Organization.

Prediction of Small for Gestational by Standard and Ultrasound–Delivery Interval	N	Area under the Curve (95% C.I.)	Sensitivity			
			FPR 5%	FPR 10%	FPR 15%	FPR 20%
Non-customized MSUH						
1 week (8–14 days)	156	0.94 (0.90–0.98)	58.3 (36.9–77.2)	75.0 (52.9–89.4)	92.0 (71.9–98.7)	96.0 (77.1–99.8)
2 weeks (15–21 days)	767	0.91 (0.88–0.94)	63.6 (53.3–72.9)	74.7 (64.8–82.7)	85.9 (77.1–91.8)	88.9 (80.6–94.1)
3 weeks (22–28 days)	1725	0.87 (0.84–0.90)	46.3 (39.1–53.7)	61.1 (53.7–68.0)	68.9 (61.7–75.3)	77.4 (70.7–83.0)
4 weeks (29–35 days)	2965	0.88 (0.86–0.90)	48.4 (42.5–54.3)	65.7 (59.9–71.1)	75.4 (69.9–80.2)	81.0 (75.9–85.3)
5 weeks (36–42 days)	2596	0.84 (0.81–0.87)	32.5 (26.1–39.6)	52.1 (44.8–59.3)	65.5 (58.3–72.1)	71.6 (64.6–77.7)
6 weeks (43–49 days)	1276	0.81 (0.77–0.85)	26.0 (17.8–36.1)	41.7 (31.9–52.2)	53.1 (42.7–63.3)	65.6 (55.1–74.8)
Customized MSUH						
1 week (8–14 days)	156	0.92 (0.86–0.98)	58.3 (36.9–77.2)	79.2 (57.3–92.1)	83.3 (61.8–94.5)	91.7 (71.6–98.6)
2 weeks (15–21 days)	767	0.89 (0.85–0.92)	56.6 (46.3–66.4)	68.7 (58.5–77.4)	77.8 (68.1–85.3)	79.8 (70.3–86.9)
3 weeks (22–28 days)	1725	0.82 (0.79–0.85)	35.3 (28.6–42.6)	51.6 (44.3–58.9)	58.4 (51.0–65.4)	68.4 (61.2–74.8)
4 weeks (29–35 days)	2965	0.84 (0.82–0.86)	40.1 (34.4–46.0)	55.7 (49.8–61.5)	66.8 (61.0–72.1)	73.0 (67.4–78.0)
5 weeks (36–42 days)	2596	0.78 (0.74–0.81)	25.3 (19.5–32.1)	40.7 (33.8–48.0)	52.6 (45.3–59.8)	58.8 (51.5–65.7)
6 weeks (43–49 days)	1276	0.76 (0.71–0.80)	21.9 (14.4–31.7)	39.6 (29.9–50.1)	47.9 (37.7–58.3)	55.2 (44.7–65.2)
Figueras						
1 week (8–14 days)	156	0.91 (0.85–0.96)	54.2 (33.3–73.9)	66.7 (44.7–83.6)	79.2 (57.3–92.1)	87.5 (66.5–96.7)
2 weeks (15–21 days)	767	0.89 (0.85–0.92)	56.6 (46.3–66.4)	65.7 (55.4–74.8)	79.8 (70.3–86.9)	83.8 (74.7–90.2)
3 weeks (22–28 days)	1725	0.82 (0.79–0.85)	37.4 (30.6–44.7)	48.9 (41.6–56.2)	61.6 (54.3–68.5)	65.8 (58.5–72.4)
4 weeks (29–35 days)	2965	0.83 (0.81–0.86)	37.0 (31.5–42.9)	51.2 (45.3–57.1)	63.0 (57.1–68.5)	72.3 (66.7–77.3)
5 weeks (36–42 days)	2596	0.77 (0.74–0.81)	26.8 (20.8–33.7)	42.3 (35.3–49.6)	50.5 (43.3–57.7)	57.7 (50.6–64.7)
6 weeks (43–49 days)	1276	0.74 (0.70–0.79)	20.8 (13.5–30.5)	35.4 (26.1–45.9)	42.7 (32.8–53.2)	51.0 (40.7–61.3)
INTERGROWTH–21st						
1 week (8–14 days)	156	0.92 (0.87–0.96)	37.5 (19.6–59.2)	66.7 (44.7–83.6)	79.2 (57.3–92.1)	87.5 (66.5–96.7)
2 weeks (15–21 days)	767	0.89 (0.86–0.92)	54.5 (44.2–64.5)	70.7 (60.6–79.2)	76.8 (67.0–84.4)	81.8 (72.5–88.6)
3 weeks (22–28 days)	1725	0.84 (0.81–0.87)	38.4 (31.5–45.7)	55.8 (48.4–62.9)	63.7 (56.4–70.5)	72.6 (65.6–78.7)
4 weeks (29–35 days)	2965	0.87 (0.85–0–89)	41.5 (35.8–47.4)	62.6 (56.7–68.1)	73.3 (67.7–78.2)	79.9 (74.7–84.3)
5 weeks (36–42 days)	2596	0.82 (0.79–0.85)	32.5 (26.1–39.6)	49.0 (41.8–56.2)	61.3 (54.0–68.1)	68.0 (60.9–74.4)
6 weeks (43–49 days)	1276	0.79 (0.74–0.83)	17.7 (10.9–27.1)	34.4 (25.2–44.9)	51.0 (40.7–61.3)	56.2 (45.7–66.2)

Table 5. *Cont.*

Prediction of Small for Gestational by Standard and Ultrasound–Delivery Interval	N	Area under the Curve (95% C.I.)	Sensitivity			
			FPR 5%	FPR 10%	FPR 15%	FPR 20%
WHO						
1 week (8–14 days)	156	0.92 (0.87–0.97)	42.5 (23.5–63.8)	83.3 (61.8–94.5)	95.8 (76.8–99.8)	95.8 (76.8–99.8)
2 weeks (15–21 days)	767	0.89 (0.86–0.93)	59.6 (49.2–69.2)	71.7 (61.6–80.1)	71.7 (61.6–80.1)	78.8 (69.2–86.1)
3 weeks (22–28 days)	1725	0.86 (0.83–0.89)	44.7 (37.6–52.1)	60.5 (53.1–67.4)	66.3 (59.0–72.9)	74.2 (67.2–80.1)
4 weeks (29–35 days)	2965	0.85 (0.82–0.87)	35.6 (30.1–41.5)	57.1 (51.2–62.8)	63.3 (57.4–68.8)	74.4 (68.9–79.2)
5 weeks (36–42 days)	2596	0.82 (0.79–0.84)	30.4 (24.1–37.5)	47.9 (40.7–55.2)	52.6 (45.3–59.8)	61.3 (54.0–68.1)
6 weeks (43–49 days)	1276	0.77 (0.72–0.82)	28.1 (19.6–38.3)	39.6 (29.9–50.1)	44.8 (34.7–55.3)	57.3 (46.8–67.2)
Fetal Medicine Foundation						
1 week (8–14 days)	156	0.94 (0.89–0.98)	58.3 (36.9–77.2)	75.0 (52.9–89.4)	91.7 (71.6–98.6)	95.8 (76.8–99.8)
2 weeks (15–21 days)	767	0.91 (0.88–0.94)	59.6 (49.2–69.2)	74.7 (64.8–82.7)	84.8 (75.9–91.0)	87.9 (79.4–93.3)
3 weeks (22–28 days)	1725	0.87 (0.84–0.90)	44.7 (37.6–52.1)	61.1 (53.7–68.0)	70.0 (62.9–76.3)	77.9 (71.2–83.4)
4 weeks (29–35 days)	2965	0.88 (0.86–0.90)	45.3 (39.5–51.2)	66.8 (61.0–72.1)	75.1 (69.6–79.9)	79.9 (74.7–84.3)
5 weeks (36–42 days)	2596	0.84 (0.81–0.86)	33.5 (27.0–40.7)	52.6 (45.3–59.8)	64.4 (57.2–71.0)	71.1 (64.1–77.3)
6 weeks (43–49 days)	1276	0.81 (0.77–0.85)	28.1 (19.6–38.3)	42.7 (32.8–53.2)	55.2 (44.7–65.2)	63.5 (53.0–72.9)

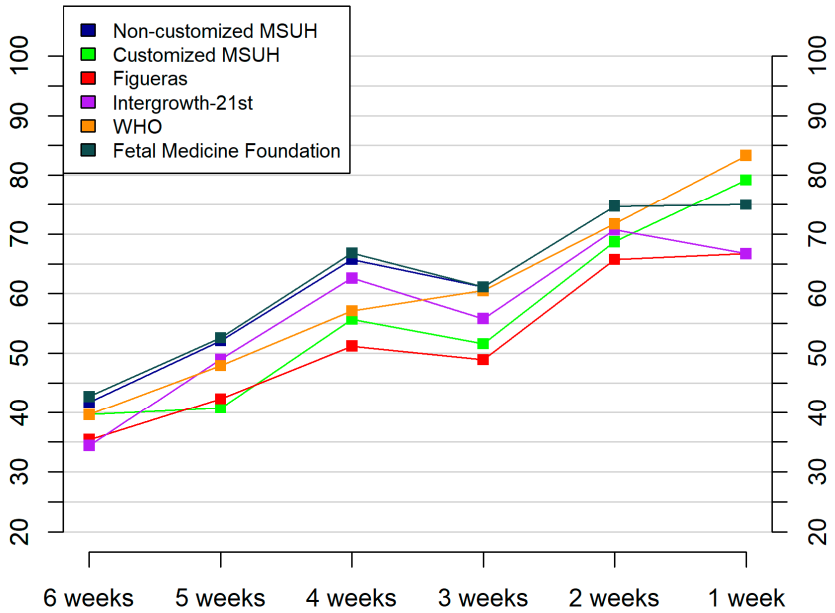

Figure 5. Prediction of small for gestational age cases, by standard and by ultrasound–delivery interval (1–6 weeks), for a 10% false positive rate. Growth standards: non-customized Miguel Servet University Hospital (MSUH), customized MSUH, Figueras et al., INTERGROWTH-21st, World Health Organization (WHO), and Fetal Medicine Foundation.

Figure 6 displays odds ratios and 95% confidence intervals of the standards in order to predict SGAs by ultrasound–delivery interval (range 1–6 weeks). Figure 7 illustrates the receiver operating characteristic curve comparison of fetal growth standards for the prediction of SGA newborns according to the ultrasound–delivery interval (range 1–6 weeks).

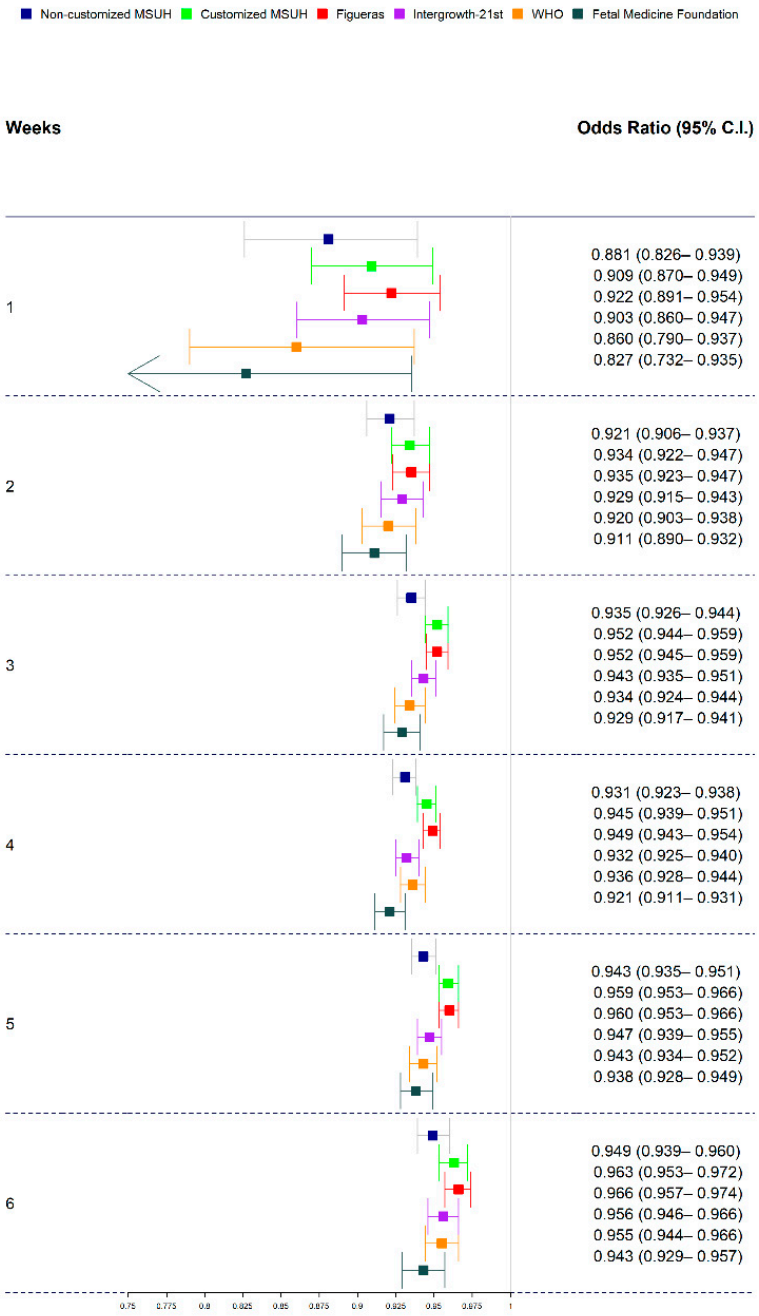

Figure 6. Odds ratios (ORs), 95% confidence intervals (CIs), and *p*-values of standards, in order to predict small for gestational age (SGA) fetuses by standard and ultrasound–delivery interval delivery date (1–6 weeks). Growth standards: non-customized Miguel Servet University Hospital (MSUH), customized MSUH, Figueras et al., INTERGROWTH-21st, World Health Organization (WHO), and Fetal Medicine Foundation.

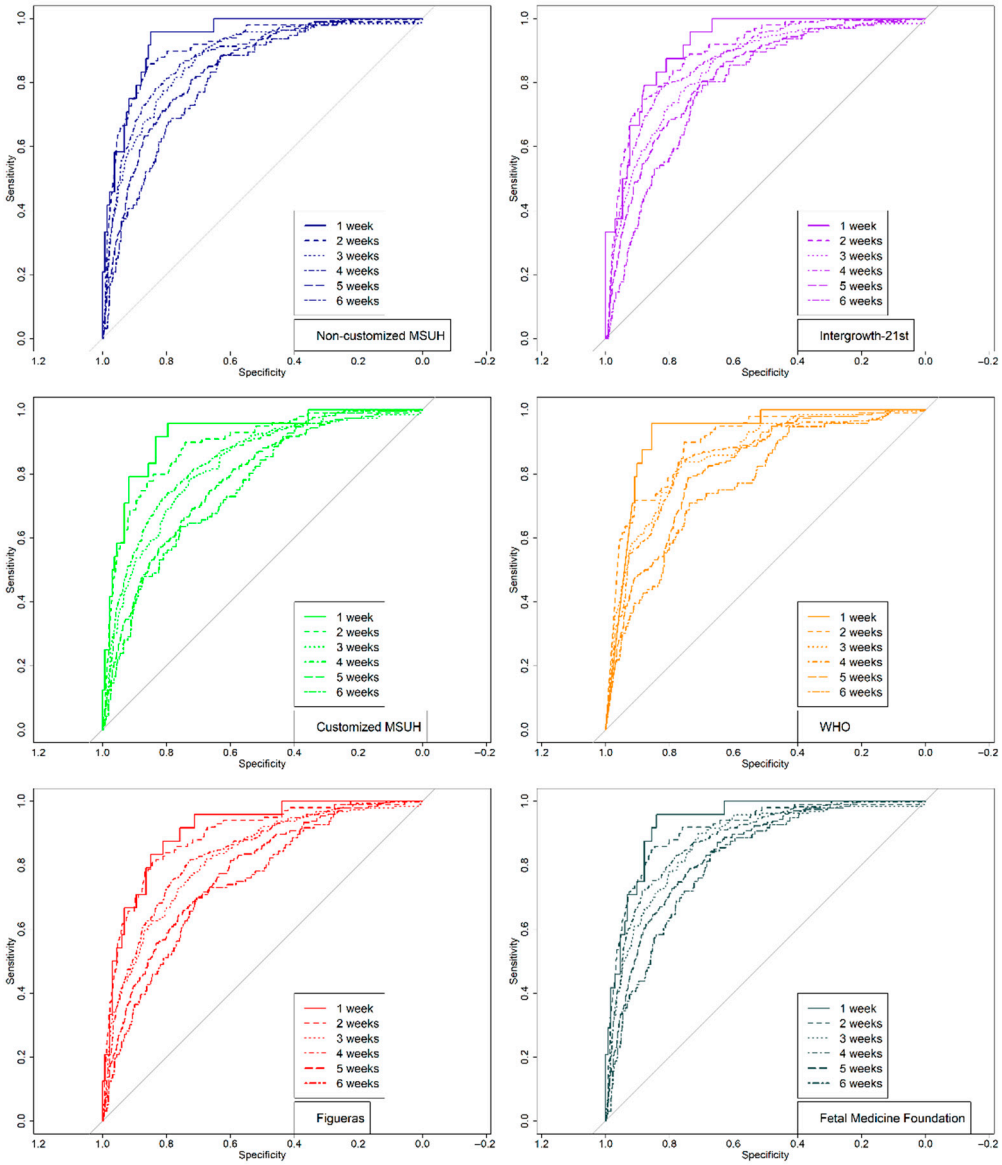

Figure 7. Receiver operating characteristic curves: comparison of fetal growth standards and area under the curve for prediction of small for gestational age (SGA) by standard and by ultrasound–delivery interval (1–6 weeks). Growth standards: non-customized Miguel Servet University Hospital (MSUH), customized MSUH, Figueras et al., INTERGROWTH-21st, World Health Organization (WHO), and Fetal Medicine Foundation.

4. Discussion

4.1. Principal Findings

We have demonstrated the utility of EPW by ultrasound at 35 weeks (range 34+0–36+6 weeks) as a predictor of SGA fetuses at delivery at term. Adjusting the percentile threshold points, the growth standards showed a similar good predictive ability, but with a significant advantage for the non-customized MSUH and Fetal Medicine Foundation standards, and a disadvantage for both the customized MSUH and Figueras standards, for SGA fetuses.

In our results, we found an underestimation of 10th percentile, by ultrasound at 35 weeks (range 34–36 weeks) with the WHO (7.5%) and FMF (2.7%) standards, and an overestimation with the Figueras (18.1%) standard; for that, we can conclude that these standards have a lack of calibration for our study population. The MSHU (NC (11.9%) and customized (12.2%)) and INTERGROWTH-21st (12.7%) standards fit better to the 10th percentile, with a minimum error, probably for the exclusion of premature deliveries.

When we analyzed the APO-predictive ability of the six standards by percentile weight <10 at 35th week of gestational age, the customized Fetal Medicine Foundation and WHO standards showed the greatest diagnostic ability, with statistically significant differences from the rest of standards. The main reason for this lies in the greater proportion of 10th percentile EPW for the Fetal Medicine Foundation (21.2%) and WHO (12.6%) standards, In any case, with similar proportions of EPW < 10, the non-customized MSUH and INTERGROWTH-21st standards show a better APO-predictive ability than the customized MSUH and Figueras standards. A previous study did not find any significant differences between the customized and non-customized standards when analyzing the predictive ability of EPW to detect APOs; by contrast, using EPW > 90th percentile, we detected significant differences [34].

4.2. Prediction by Fetal Biometry and Ultrasound–Delivery Interval

There is no international consensus on performing a universal ultrasound in the third trimester; two international guidelines—the RCOG [35], and the American College of Obstetrics and Gynecology (ACOG) [36]—do not recommend universal ultrasound to detect fetal growth anomalies. Sovio el al [37], however, found that universal third trimester ultrasound in nulliparous women, compared with selected ultrasound, tripled the detection of SGA < P10 infants, and could identify FGR fetuses at increased risk of neonatal morbidity.

The EPW at third trimester ultrasound over 32 weeks has been shown to be a good predictive model (AUC > 0.85) for the detection of SGA at delivery in several studies, although with detection rates limited for late-onset SGA births [4,38,39]. For gestational time, the detection rate of SGA at delivery by ultrasound between 33–34 weeks is approximately 52%, and between 36–37 weeks it is approximately 60% (FPR of 10%) [40–42]. According to several studies, therefore, detection is higher the later the ultrasound is performed [14,43,44]. In our case, the predictive capacity for SGA at delivery by ultrasound at 35 weeks is also limited for the six growth standards, and generally, a shorter ultrasound–delivery interval is correlated with better prediction rates. In any case, the cutoff points of the 10th percentiles by ultrasound at 35 weeks are moderate for the prediction of SGA at delivery.

4.3. Prediction by Fetal Biometry and Ultrasound–Delivery Interval: Comparison of Standards

Blue et al., in 2018 [45], compared the RCOG and ACOG standards for the detection of SGA at delivery, with a mean birth of 37.7 weeks and ultrasounds performed in the previous 2 weeks, and showed that both standards had a moderate predictive capacity (AUCs of 0.78 and 0.76, respectively). In another study by Blue in 2019 [46], the Hadlock and INTERGROWTH-21st standards for the detection of SGA, with deliveries at 37 weeks on average and ultrasound in the previous two weeks, showed good predictive capabilities (>0.90), with cutoff points of the optimal percentile at 15% for the Hadlock standard and 22% for the INTERGROWTH-21st standard. Both studies are not comparable to ours; although they show the minimum differences in SGA prediction regardless of the standard used, neither of them studied customized standards.

In two studies by Odibo et al. in 2018 [47] and 2019 [48], using the same sample obtained for the three different standards compared (INTERGROWTH-21st, a local customized standard, and the Hadlock standard), a moderate predictive capacity for SGA at delivery was achieved (0.67, 0.62, and 0.69, respectively), although with ultrasound performed between 26 and 36+6 weeks, and an average ultrasound–delivery interval of 6.7 weeks—also different from our study.

Reboul et al., in 2017 [49], found that the Hadlock and the customized Gardosi standards had a moderate predictive capacity for SGA at delivery (0.768 and 0.708, respectively), with the detection rates somewhat higher for the Hadlock standard, although with an average of performing ultrasound at 32 weeks—lower than ours, which could justify the lower predictive capacity.

4.4. Clinical and Research Implications

In clinical practice we can say that more important than the choice of the growth standard is its calibration before clinical use, both by ultrasound and delivery, in the reference population. The physiological and non-pathological characteristics of each population are those that will allow us to calibrate the standard to be used.

There are several factors for which ultrasound in the third trimester presents limitations when predicting SGA and FGRs at delivery, and some of them are unavoidable—especially the systematic error of ultrasound at the time of EFW calculation [50]. With the current studies carried out on the timing of performing the third trimester ultrasound and the ultrasound–delivery interval, together with our comparative study of standards, we can affirm that the timing that better predicts SGA cases is the one closest to delivery; however, we cannot delay ultrasound universally to 37 weeks, since we would not detect early FGRs. As we are not currently able to make that prediction, it will continue to be the subject of future research.

According to our results, it would be appropriate to raise the ultrasound-estimated weight percentile cutoff point above 10 for fetal growth control. This is because the 10th percentile has been shown to be insufficient, and with low predictive capacity for SGA at delivery and, therefore, fetuses that can potentially be IUGR even before delivery can escape control and, thus, increase their morbidity and mortality. Our recommendation, in the ultrasound during the third trimester, between 35 and 36 weeks, could be to raise the cutoff point at least from the 10th to the 20th percentile for strict control of fetal growth.

4.5. Strengths and Limitations of the Study

Our study has several strengths, including the wide sample size close to 10,000 pregnancies. Ultrasound measurements were performed in routine clinical practice; thus, weight estimations were more concentrated over specific weeks of gestational age. Limitations of our investigation are that our data came from a single hospital, and their retrospective nature could limit the generalization of our standards. Furthermore, the information of the ultrasound was available to the obstetricians, which could mean a bias in the management of the pregnancies. A small percentage of labors are inductions of labor or cesarean sections programmed by IUGR, and they could act as confounding factors in the study. Similarly, other cases of early termination due to other causes have not been taken into account.

5. Conclusions

In summary, even with limited detection rates, the growth standards showed a similar good predictive ability, with a statistically significant improvement by the use of non-customized standards, for SGA at delivery by ultrasound at 35 weeks. Generally, a shorter ultrasound delivery interval for the different standards was correlated with better prediction rates for small gestational age cases. When focusing on the use of EPW < 10th percentile at week 35 for the prediction of APOs, non-customized standards also demonstrated an advantage over customized standards.

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Institutional Review Board Statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and approved by the Clinical Research Ethics Committee of Aragon (PI20/414).

Informed Consent Statement: Patient consent was waived, as due to the retrospective observational nature of this study, data could be fully anonymized.

Data Availability Statement: The data analyzed were retrieved from the Miguel Servet University Hospital database.

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Reduced Growth in Non-Small for Gestational Age Fetuses from 35 Weeks of Gestation to Birth and Perinatal Outcomes

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Keywords
Decreased percentile growth · Small for gestational age · Fetal growth restriction · Fetal growth velocity · Adverse perinatal outcomes

Abstract
Objective: This study aimed to assess reduced fetal growth between 35 weeks of gestation and birth in non-small for gestational age fetuses associated with adverse perinatal outcomes (APOs). ***Material and Method:*** It is a retrospective cohort study of 9,164 non-small for gestational age fetuses estimated by ultrasound at 35 weeks. The difference between the birth weight percentile and the estimated percentile weight (EPW) at 35 weeks of gestation was calculated, and we studied the relationship of this difference with the appearance of APO. APOs were defined as cesarean or instrumental delivery rates for nonreassuring fetal status, 5-min Apgar score <7, arterial cord blood pH <7.10, and stillbirth. Fetuses that exhibited a percentile decrease between both moments were classified into 6 categories according to the amount of percentile decrease (0.01–10.0, 10.01–20.0, 20.01–30.0, 30.01–40.0, 40.01–50.0, and >50.0 percentiles). It was evaluated whether the appearance of APO was related to the amount of this percentile decrease. Relative risk (RR) was calculated in these subgroups to predict APOs in general and for each APO in particular. Receiver operating characteristic and area under curves (AUC) for the difference in the percentile was calculated, used as a continuous parameter in the entire study population. ***Results:*** The median gestational age at delivery in uncomplicated pregnancies was 40.0 (39.1–40.7) and in pregnancies with APOs 40.3 (49.4–41.0), $p < 0.001$. The prevalence of APOs was greater in the group of fetuses with a decrease in percentile (7.6%) compared to those with increased percentile (4.8%) ($p < 0.001$). The RR was 1.63 (95% CI: 1.365–1.944, $p < 0.001$). Although the differences were significant in all decreased percentile groups, RRs were significantly higher when decreased growth values were >40 points (RR: 2.036, 95% CI: 1.581–2.623, $p < 0.001$). The estimated value of the AUC for percentile decrease was 0.58 (0.56–0.61, $p < 0.001$). ***Conclusion:*** Fetuses with a decrease in the EPW between the ultrasound at 35 weeks of gestation and birth have a higher risk of APOs, being double in fetuses with a decrease of >40 percentile points.

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Introduction

Prenatal ultrasound during the third trimester allows estimating the birth weight which is relevant due to the link between newborns small for gestational age (SGA) and adverse perinatal outcomes (APOs) and the risk of permanent neurological alterations [1, 2]. Most fetal growth assessment strategies rely on the cross-sectional evaluation of fetal size during the third trimester [3, 4]. Rossavik et al. [5] developed a growth model capable of specifying individual growth curve standards for several fetal anatomical parameters. However, a proportion of fetuses with weights between 10th and 90th percentile may have suboptimal growth rendering them vulnerable, increasing the risk of APOs [6]. These fetuses born with adequate gestational weight may display clinical features of placental insufficiency [7].

Karlsen et al. [8] postulated to classify pregnant women at risk of fetal growth restriction when estimated fetal weight (EFW) assessment corresponds to fetuses with a ≤5th centile for size or 10th for conditional growth, compared to those with higher centiles associated with normal fetal growth. It seems that both growth endpoints may contribute to the predictive value.

MacDonald et al. [9] reported reduced growth velocity between 28 and 36 weeks' gestation among fetuses born adequate for gestational age is associated with antenatal, intrapartum, and neonatal indicators of placental insufficiency. However, Ciobanu et al. [10] concluded that addition of estimated growth velocity between 32 and 36 weeks' gestation did not improve the diagnosis of SGA at birth and APOs. The disparity of these studies may derive from the different inclusion and exclusion criteria of their populations and methods of assessing fetal growth.

The objective of this study is to evaluate if the decrease in fetal growth in the late third trimester of gestation is associated with the appearance of APOs and if this would serve as a good parameter to predict them. And for this, we have used the weight percentile in the 35th week gestation ultrasound and the birth weight percentile, assuming that the percentile difference between both moments would be a surrogate marker of what can really be measured, which is the difference in percentiles between an ultrasound close to delivery and an ultrasound at week 35.

Methods

Study Design

We performed a retrospective cohort study of births assisted at the Miguel Servet University Hospital (MSUH) between March 2012 and December 2016. The inclusion criteria were (i) singleton pregnancies controlled at the MSUH from the first trimester of gestation, (ii) a fetal ultrasound assessment at the gestational age of 35 (range 34–36) weeks with estimated percentile weight (EPW) above the 10th percentile, and (iii) deliveries between 37 and 42 weeks of gestational age without malformations or chromosomal abnormalities. The Clinical Research Ethics Committee of Aragon (PI 18/333) approved the investigation.

Analyzed maternal characteristics included age and BMI at the beginning of pregnancy, parity, ethnicity, and smoking habits. We also collected obstetric information including infant sex, birth weight, and gestational age at birth. APOs included 5-min Apgar score <7, instrumental or cesarean delivery, arterial cord blood pH <7.10, and stillbirth or neonatal death.

Gestational age was defined by the first-trimester ultrasound exam, following the ACOG recommendations [11]. Ultrasound EFW was calculated with the Hadlock et al. [12] formula. The ultrasound weight percentile and the birth weight percentile were estimated using our nonpersonalized local population standard [13]. The birth percentile weight was calculated considering gestational age, weight, and newborn sex compared to our reference of normal pregnant women [13]. We assessed fetal growth using the difference between the percentile birth weight and EPW at 35 weeks' gestation and studied the association between percentile decrease and APOs.

Statistical Analyses

The Kolmogorov-Smirnov test was used to explore in the cohort if the analyzed variables display a normal distribution. As the test rejected normality for some variables, we reported data as the median and interquartile range for continuous variables. Absolute and relative frequencies were reported for categorical variables. The differences between the groups with and without APOs were analyzed using the nonparametric Mann-Whitney test for quantitative variables and the χ^2 test for qualitative variables.

Fetuses were classified according to APOs and to the percentile decrease in 2 groups, yes or no (qualitative dichotomous variable). The χ^2 test of independence was used to find associations among these variables. Taking as control the group of no decrease in percentile, we assessed whether the appearance of APOs was related to the greater or lesser percentile decrease to try and determine a cutoff point where the appearance of APOs became more significant.

Besides, to quantify the association between decreasing fetal weight trajectories and APOs, we estimated the relative risk (RR) of percentile decreases. Fetuses presenting a decrease in percentile between the 35th week ultrasound exam and birth were classified into 6 categories according to the magnitude of the percentile decline compared to birth weight percentile (0.01–10.0, 10.01–20.0, 20.01–30.0, 30.01–40.0, 40.01–50.0, and >50.01). RRs and *p* values were estimated defining different groups of percentile decrease taking as cutoff points the values of 0, 10, 20, 30, 40, and 50. We also calculated both the receiver operating characteristic (ROC) curves and the area under the curve (AUC) for the difference in percentile, used as a continuous parameter in the global study population. A test to analyze whether or not AUC is equal to 0.5 that corresponds to a chance model was performed.

Finally, we analyzed the decrease in percentile as a predictor variable in a multivariate logistic regression model to predict APOs, exploring if the loss in percentile is an independent factor

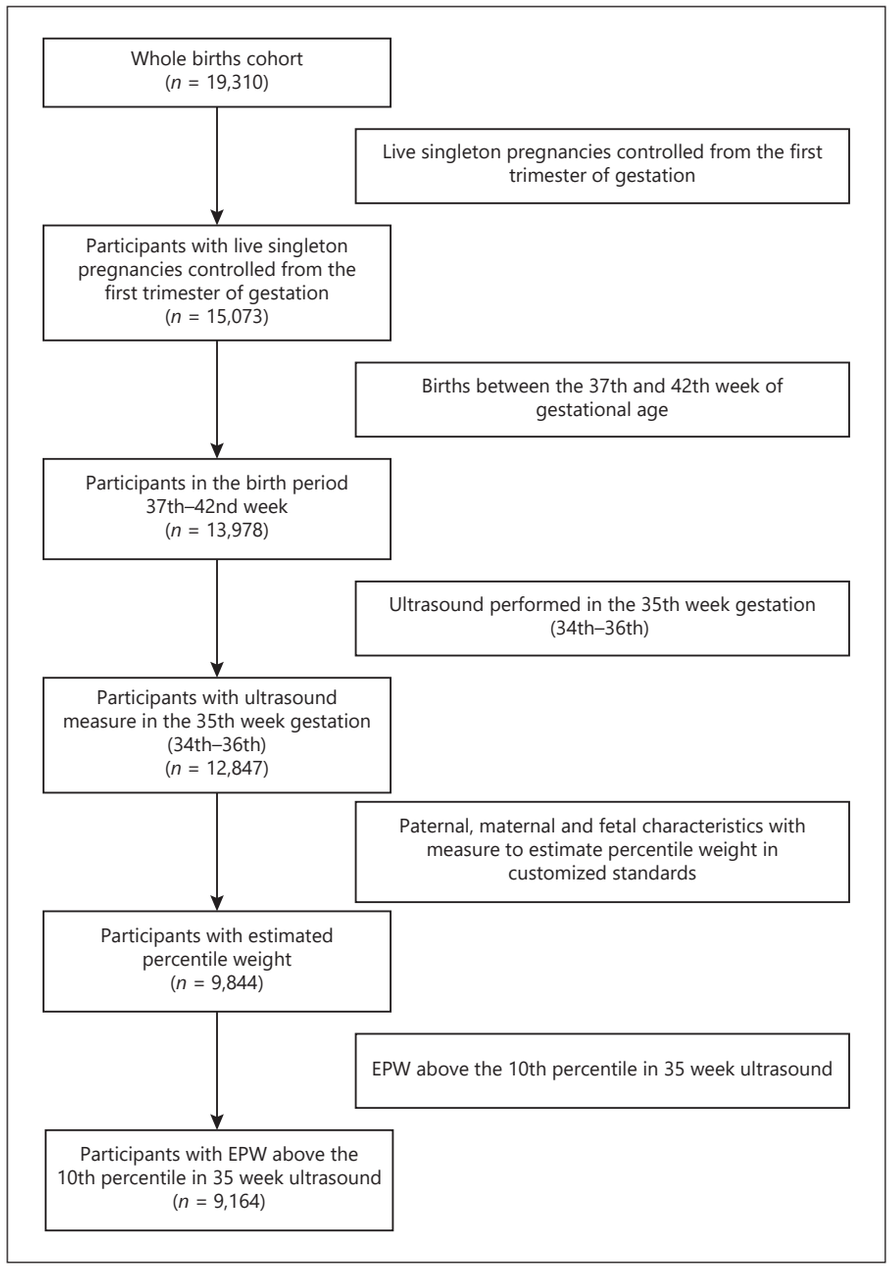

Fig. 1. Study participant selection sample. EPW, estimated percentile weight.

confronted to the maternal age, maternal height, maternal BMI, birth weight, and newborn sex. We provided a set of effects plot, and these plots show the mean of APO probability at each level of predictor variables. These plots compare the relative strength of the effects of the APO risk factors.

Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA) and R language programming version 3.6.2 (The R Statistical Foundation, Vienna, Austria). Tests were bilateral, and the threshold p value was set at 0.05.

Results

The sample studied included 9,164 fetuses with EPW above the 10th percentile in 35-week ultrasound (shown in Fig. 1). Table 1 shows participants' descriptive characteristics. Women with APOs ($n = 581$) had higher rates of both nulliparity ($p < 0.001$) and higher first trimester BMI ($p < 0.001$) compared to controls ($n = 8,583$). There was no significant neonate gender difference in the preva-

Table 1. Parental baseline characteristics and pregnancy and perinatal characteristics of uncomplicated pregnancies (n = 8,583) and pregnancies with APOs (n = 581)

Clinical characteristics	Uncomplicated pregnancies (n = 8,583)	Pregnancies with APOs (n = 581)	p value*
Parental characteristics			
Maternal age, years	33.3 (30.0–36.0)	33.7 (30.2–36.3)	0.07
Maternal BMI	23.3 (21.2–26.3)	24.0 (21.5–27.4)	<0.001
Parity			
0	4,350 (50.7)	404 (69.5)	
1	3,480 (40.6)	144 (24.8)	<0.001
≥2	748 (8.7)	33 (5.7)	
Maternal ethnicity			
Caucasian	8,256 (96.2)	561 (96.6)	
Asian	226 (2.6)	17 (2.9)	0.321
African	101 (1.2)	3 (0.5)	
Maternal smoking habits			
Yes	1,346 (15.7)	90 (15.5)	0.902
No	7,237 (84.3)	491 (84.5)	
Ultrasound parameters at 35 (34–36) weeks			
Gestational age at ultrasound, weeks	35.0 (35.0–35.3)	35.0 (35.0–35.3)	0.393
EFW by the Hadlock et al. [12] formula, g	2,522.3 (2,362–2,716)	2,486 (2,325–2,684)	0.002
EPW	57.2 (34.4–80.8)	53.4 (31.7–77.1)	0.005
Maternal and perinatal outcomes			
Gestational age at delivery	40.0 (39.1–40.7)	40.3 (39.4–41.0)	<0.001
Newborn gender			
Female	4,149 (48.3)	267 (46.0)	0.266
Male	4,434 (51.7)	314 (54.0)	
Average birth weight	3,360.0 (3,100–3,620)	3,250.0 (3,000–3,550)	<0.001
Average percentile birth weight	57.2 (32.8–79.9)	43.3 (19.8–70.0)	<0.001
Instrumental delivery for NRFS	0 (0.0)	148 (25.5)	
Cesarean delivery for NRFS	0 (0.0)	220 (37.9)	
5-min Apgar score <7	0 (0.0)	36 (6.3)	
Arterial cord blood pH <7.10	0 (0.0)	241 (41.5)	
Neonatal death	0 (0.0)	1 (7.1)	
Stillbirth	0 (0.0)	13 (92.9)	

Results are reported as medians (interquartile range) for quantitative variable and as n (%) for qualitative variables. The Mann-Whitney test was used for quantitative variables and the χ^2 test for qualitative variables. APOs, adverse perinatal outcomes; BMI, body mass index; EFW, estimated fetal weight; EPW, estimated percentile weight; NRFS, nonreassuring fetal status.

lence of APOs (p = 0.266). Median birth weight was lower in 581 cases (3,250 [3,000–3,550]) than in 8,583 controls (3,360 [3,100–3,620]), $p < 0.001$. The prevalence of APOs was 6.3% in the entire population, including infants with a 5-min Apgar score <7 (0.4%), percentages of instrumental (1.6%) or cesarean deliveries (2.4%) for nonreassuring fetal status, arterial cord blood pH <7.10 (2.6%), and stillbirth (0.15%).

Table 2 shows the association between decrease in percentile growth and APOs. Fetuses with decreased weight percentiles (n = 383; 7.6%) have more APOs compared to those with increased percentile (n = 198; 4.8%), and this

Table 2. Relationship between percentile decrease (qualitative) and appearance of APOs

Variable percentile decrease	Appearance of APOs		
	no, n (%)	yes, n (%)	p value
No	3,924 (95.2)	198 (4.8)	<0.001
Yes	4,659 (92.4)	383 (7.6)	RR: 1.629 95% CI: 1.365–1.944

χ^2 test of independence. APOs, adverse perinatal outcomes.

Table 3. Relationship between subgroups of percentile decrease (qualitative) and appearance of APOs

Amount of percentile decrease	No, *n* (%)	Yes, *n* (%)	Decrease	RR (95% CI)	*p* value
No decrease	3,925 (95.2)	198 (4.8)			
0.01–10.0	1,703 (94.0)	109 (6.0)	>0: <0	1.582 (1.339–1.864)	<0.001
10.01–20.0	1,249 (92.0)	109 (8.0)	>10: <10	1.640 (1.402–1.919)	<0.001
20.01–30.0	802 (92.6)	64 (7.4)	>20: <20	1.545 (1.300–1.837)	<0.001
30.01–40.0	482 (92.0)	42 (8.0)	>30: <30	1.707 (1.391–2.093)	<0.001
40.01–50.0	231 (86.8)	**35 (13.2)**	>40: <40	2.036 (1.581–2.623)	<0.001
>50.0	192 (88.9)	**24 (11.1)**	>50: <50	1.785 (1.214–2.625)	<0.001

Relative risk of having a growth decrease above versus equal or below each threshold. APOs, adverse perinatal outcomes.

Table 4. Relative risk of each amount of percentile decrease divided in each particular APO

Cut point	5-min Apgar score <7	Instrumental delivery for NRFS	Cesarean delivery for NRFS	Arterial cord blood pH <7.10	Stillbirth
0.0	1.868 (0.920–3.791)	**2.544 (1.752–3.695)**	**1.403 (1.070–1.810)**	**1.357 (1.050–1.754)**	1.472 (0.494–4.388)
10.0	1.841 (0.959–3,534)	**2.162 (1.569–2.978)**	**1.531 (1.178–1.990)**	**1.456 (1.134–1,870)**	1.021 (0.342–3.044)
20.0	1.719 (0.847–3.486)	**2.174 (1.559–3.030)**	1.206 (0.887–1.639)	**1.400 (1.057–1.855)**	1.063 (0.297–3.804)
30.0	1.314 (0.512–3.373)	**2.327 (1.589–3.408)**	1.381 (0.954–1.997)	**1.654 (1.190–2.299)**	1.352 (0.303–6.031)
40.0	2.250 (0.799–6.337)	**2.653 (1.654–4.257)**	**1.703 (1.073–2.701)**	**1.892 (1.244–2.879)**	3.002 (0.674–13.377)
50.0	**3.756 (1.161–12.152)**	2.057 (0.975–4.341)	1.767 (0.919–3.396)	1.600 (0.834–3.072)	**6.905 (1.555–30.665)**

APO, adverse perinatal outcome; NRFS, nonreassuring fetal status.

is statistically significant ($p < 0.001$). This association has an RR of 1.63, 95% CI: 1.365–1.944 ($p < 0.001$).

Table 3 shows results from fetuses who have decreased growth percentiles from the 35-week ultrasound to birth (5,042 fetuses) separated into 6 categories according to the magnitude of the percentile decrease between 0.01–10.0, 10.01–20.0, 20.01–30.0, 30.01–40.0, 40.01–50.0, and >50 percentiles. We analyzed the RRs of percentile decrease, taking as cutoff points to define the groups the values of 0, 10, 20, 30, 40, and 50. Although the differences are significant in all groups, RRs were highly significant when decreased growth values were >40 points (RR: 2.036, 95% CI: 1.581–2.623, $p < 0.001$) (shown in Table 3).

We also analyzed each APO individually and its relationship with the percentile decrease (shown in Table 4). Concerning 5-min Apgar score <7 points, as the number of percentile drop points increases, the RR progressively increases (decrease of 10 points RR 1.87, 95% CI: 0.92–3.79; a decrease of 50 points RR 3.76, 95% CI: 1.16–12.15). A decrease in the percentile from the 35-week ultrasound to birth is a risk factor for instrumental delivery for nonreassuring fetal status, regardless of this decrease, and this is always located with a value above 2. The same as with cesarean delivery for nonreassuring fetal status, which maintains a similar RR value in all percentile decrease groups. Regarding arterial cord blood pH <7.10, the more the percentile decreases, the greater the RR for the cited APO. And the same for stillbirth, which reaches a value of 6.90, 95% CI: 1.55–30.66 when the percentile decrease is >50.

Figure 3 displays ROC curves when percentile growth deviation is used as a continuous parameter to predict APOs in the entire study population. The value obtained for the AUC in the global population is 0.58 (95% CI: 0.56–0.61, $p < 0.001$) for the difference between the percentile birth weight and EPW at 35 weeks' gestation.

The multivariate analysis shown in Table 5 reported maternal age (OR: 1.03; $p < 0.001$), maternal height (OR: 0.979; $p = 0.003$), maternal BMI (OR: 1.045; $p < 0.001$), parity (OR: 0.433 and 0.430; $p < 0.001$ and $p < 0.001$), and a nonlinear relation with birth weight ($p = 0.002$, 0.004) as significant predictors of APOs. The decrease in percentile showed significance in the categories 10–20 (OR: 1.357; $p = 0.031$), 40–50 (OR: 2.133; $p < 0.001$), and >50 (OR: 1.623; $p = 0.043$). These results are in concordance with previous analysis: a decrease in percentile >40 is an independent predictor of APO occurrence.

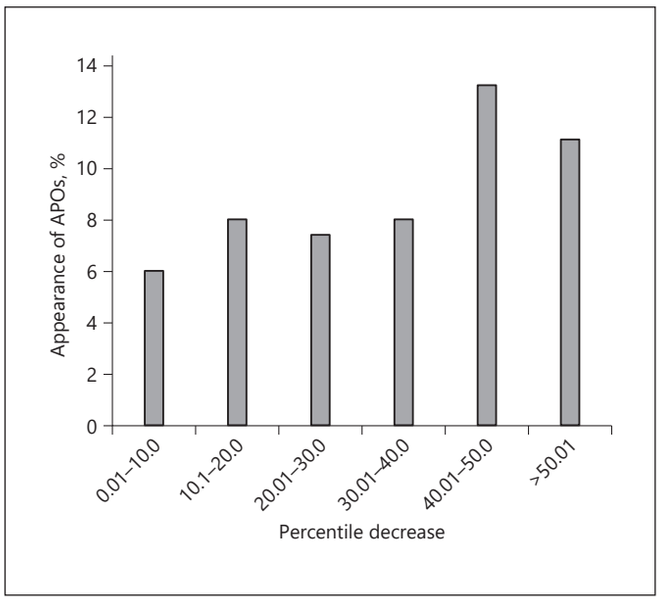

Fig. 2. Relationship between subgroups of percentile decrease (qualitative) and appearance of APOs in global population. APOs, adverse perinatal outcomes.

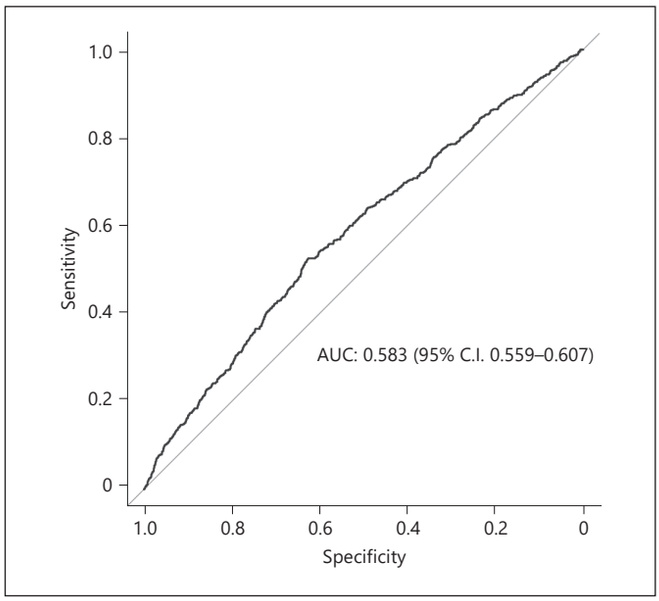

Fig. 3. ROC curve when variable percentile growth deviation is used as a parameter to predict the adverse perinatal outcomes in the global study population. ROC, receiver operating characteristic; AUC, area under the curve.

Additionally, in Figure 4, the effect plot quantified the increase in APO occurrence probability depending on multivariate predictor variables. APO probability increased with greater decrease in weight percentile. Also, the APO probability increased with greater maternal age and BMI and lower maternal height. Nulliparous women and high or very low birth weight corresponded with greater APO probability too.

Table 5. Multivariate model to predict APOs

Variable	OR (95% CI)	*p* value
Percentile decrease (Ref: <0)		
0.01–10.0	1.089 (0.851–1.392)	0.499
10.01–20.0	1.357 (1.026–1.725)	0.031
20.01–30.0	1.227 (0.878–1.615)	0.274
30.01–40.0	1.282 (0.892–1.844)	0.179
40.01–50.0	2.133 (1.414–3.159)	<0.001
>50.0	1.623 (1.106–2.593)	0.043
Maternal age (1 year)	1.035 (1.016–1.054)	<0.001
Maternal height (1 cm)	0.979 (0.966–0.993)	0.003
BMI (1)	1.045 (1.027–1.063)	<0.001
Parity (Ref: 0)		
1	0.433 (0.353–0.529)	<0.001
2	0.430 (0.291–0.613)	<0.001
Poly (birth weight, 1) (1 g)	*	0.004
Poly (birth weight, 2) (1 g)	*	0.002
Newborn sex (Ref: male)	1.151 (0.204–6.480)[&]	0.112

OR, odds ratio; CI, confidence interval; APOs, adverse perinatal outcomes. * Nonlinear dependence. [&] Variable not included in the final model.

Discussion

Principal Findings

The results of this study demonstrate that fetuses with decreased percentile growth between 35 weeks of gestation and birth have a greater frequency of APOs. We observed that fetuses with decreased growth potential in the late third trimester are at risk for APOs, and other studies support this premise [6].

The aim of the third-trimester universal screening ultrasound is to detect fetal growth anomalies, as these have been shown to have a higher frequency of APOs and long-term morbidity [14, 15]. The utility of EPW as a predictor of APOs in a large population of singleton pregnant women studied by ultrasound at 35 weeks and delivering at term has been demonstrated [16]. Other studies have shown that an early diagnosis of SGA in the third trimester can help to reduce APOs, reflecting the benefit of prenatal diagnosis in these cases [17, 18].

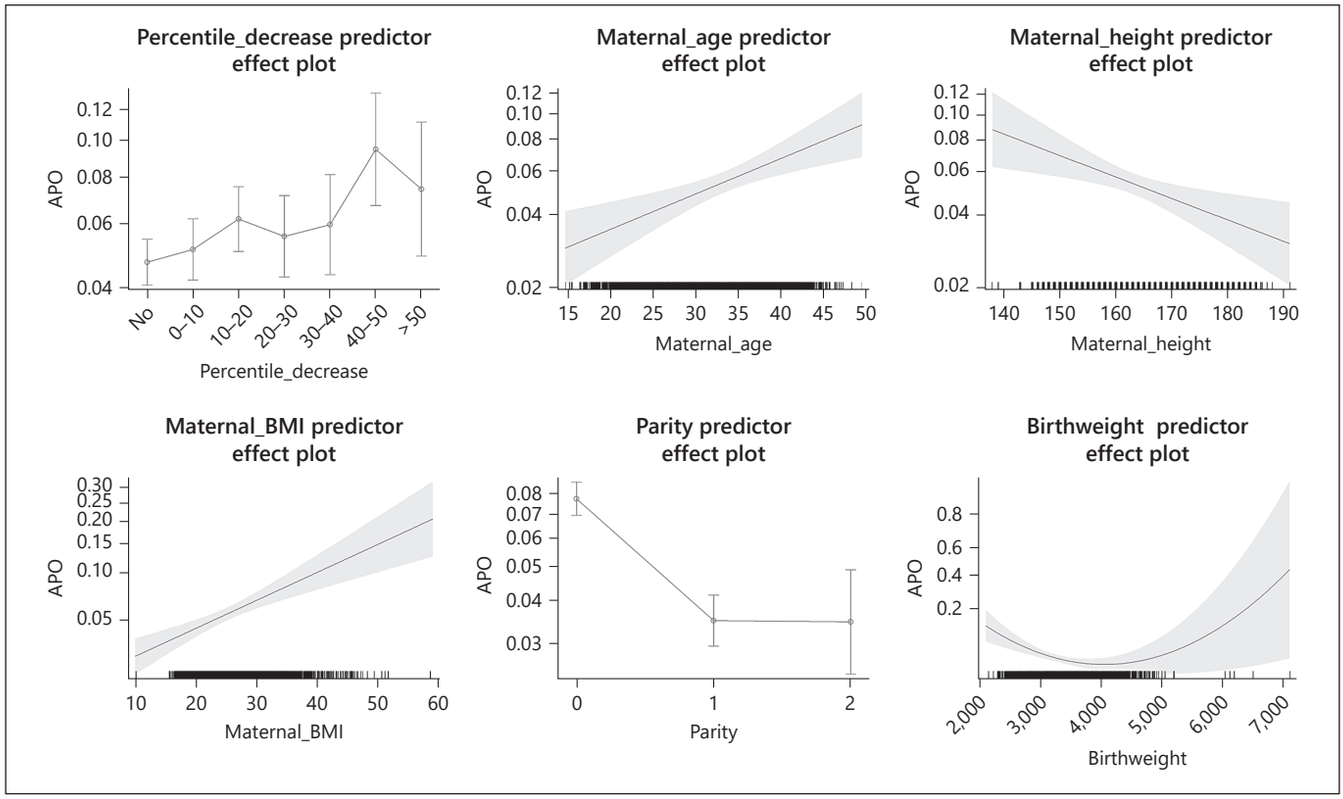

Fig. 4. APO predictor's effects plot. APO, adverse perinatal outcome.

Ganzevoort et al. [19] suggested that the use of dichotomization at the 10th percentile to define normal versus abnormal fetal growth was a limitation for ultrasound as a single diagnostic test to predict APOs. However, Deter et al. [20] previously introduced the term individualized growth assessment that establishes standards for each anatomical parameter in a fetus or neonate (an individual is its control) and identifies growth pathology as deviations from these standards, using either a single parameter or a set of parameters. This approach requires at least 2 anthropometric measures separated in time with a minimum time difference of 2–3 weeks [21].

The definition of a fetus with intrauterine growth restriction (IUGR) is internationally defined as EFW or abdominal circumference less than the third percentile, or EFW or abdominal circumference between percentile 3 and 10 with cerebral, placental, or uterine Doppler anomalies. However, recent publications endorsed by the ISUOG expand the ultrasound challenge to detect fetuses with IUGR who have not yet reached a weight below the 10th percentile. Sovio et al. [22, 23] in 2015 and 2018 and Deter et al. [20] in 2017 reported that the fetal growth velocity or percent growth deviation, independent of the population table used (universal, local, prescriptive, or descriptive), is more relevant than EFW by screening ultrasound to determine intrauterine growth disorders [24]. Also, Bligh et al. [6] in 2019 suggested that some fetuses exhibit a subtle decline in growth velocity at term which may be responsible for the increased risk of intrapartum compromise and APOs. Indeed, in infant cases, growth velocity in early infancy has been repeatedly demonstrated to be a better predictor of subsequent weight than any other cross-sectional measurement [25]. Other authors have associated the third-trimester fetal growth velocity with the appearance of adverse effects [4, 9, 22]. This finding is consistent with our work, which showed a higher frequency of APOs in the group of fetuses with a decrease in percentile weight from 35 weeks of gestation to birth.

When we analyzed the growth rate in the third trimester of gestation in the entire population in relation to the appearance of APOs, we observed that the lower the growth rate, the greater the frequency of APOs. In our study, a decrease >40 centiles is remarkable, which could

be established as a possible cutoff point to detect the population at risk of APOs (Fig. 2). Our RR is 2.04 (95% CI: 1.58–2.62, $p < 0.001$), which is approximately twice that of the normal population and consistent with MacDonald et al. [9] data. These authors also showed an association between neonatal acidosis and a decrease of >35 centiles in fetuses born at a normal birth weight. Furthermore, a decrease of >2 quartiles (or >50 centiles) has been recommended by consensus criteria for IUGR [24].

Sovio et al. [23] in 2018 failed to find a significant association between second- to third-trimester slow abdominal circumference growth velocity and adverse outcome (RR 1.36; 95% CI: 0.97–1.90) in a cohort of unselected nulliparous women, and this association was even smaller when only babies born with a normal birth weight were considered. By contrast, we have observed significant differences and a greater RR in the group with percentile decrease between 35 weeks of gestation and birth (RR: 1.63, 95% CI: 1.36–1.94 in the global population vs. RR: 2.04, 95% CI: 1.58–2.62 in fetuses with EFW below the 40th percentile). The disparity of the 2 studies may be related to the period of pregnancy analyzed due to the differences in early and late placental insufficiency.

We found that any percentile decrease is a risk factor for each APO in particular. Our results agree with recent publications from Chatzakis et al. [26] or Pacora et al. [27]. In the article by Chatzakis et al. [26], a fetal growth deceleration ≥50th percentile in non-SGA fetuses was associated with increased risk for neonatal intensive care unit admission (OR 1.8) and perinatal death (OR 3.8). Pacora et al. [27] found that a fetus with a decline of EFW percentile velocity <50th percentile among controls has a 4.7-fold increased risk to die antepartum, which is similar to our results.

It should be highlighted that the estimated value of the area under the ROC curve for percentile decrease showed a poor discriminative ability and low detection rate of APOs. This is concordant with the exploratory study of Hutcheon et al. [28] in 2010 that failed to observe any benefits of using conditional growth percentiles instead of EPW to identify APOs due to growth restriction. This was also supported by the small contribution of growth velocity to EFW at 35–36 weeks for the prediction of SGA neonates and APOs observed by Ciobanu et al. [10] in 2019. Just like Hiersch et al. [29], who in their publication concluded that serial ultrasound evaluations either by calculating fetal growth velocity, conditional percentiles, projection-based methods, or individual growth assessment seem promising to detect IUGR with increased risk of adverse perinatal events in high-risk pregnancies, however, in low-risk pregnancies remain unclear.

Presently, there is a consensus that the best prediction of an SGA neonate is achieved by routine ultrasound examination at 35–37 weeks' gestation [10, 30, 31]. We previously reported that the predictive capacity of universal ultrasound screening for APOs of EFW in the third trimester is limited and is similar, regardless of the standard used (local, universal, customized, prescriptive, or descriptive) [16]. It seems likely that the 10th percentile threshold point has limited capacity to predict APOs.

In the period studied (2012–2016), we maintained dichotomization at the 10th percentile to screen fetal growth restriction, and we raised the threshold to 15th percentile from 2017; meanwhile, Iliodromiti et al. [32] recommended to fix the 25th percentile cutoff at delivery for the detection of APOs, since the 10th percentile was very restrictive. We analyzed the relationship between fetal growth and APOs in various subgroups of percentile decrease between 35 weeks of gestation and birth, finding that the group of fetuses with percentile decrease of >40 points was twice as likely to suffer APOs although the risk did not increase linearly as EPW.

In our cohort, approximately 6% of patients were controlled above 37 weeks per low weight percentiles. On the other hand, our percentage of labor induction was approximately 27%, of which 1.6% was due to growth defects. In any case, maybe there were other factors (advanced age, smokers, and biochemical factors) that could be associated with a fall of percentile at the end of pregnancy, and future research directions should determine which fetuses above the 10th percentile at 35 weeks would benefit of ultrasound repetition to detect those at risk of late decreased growth and therefore with greater risk of APOs. In addition, maternal and fetal parameters remain to be determined since fetal growth velocity alone has a poor sensitivity to detect APOs.

Strengths and Limitations

The main strength of this study is the large sample size and participants with broad ranges of characteristics. This study reflects the population of women at term in our institution and suggests that our findings may be applicable and relevant to other similar healthcare settings. Additionally, the overall spontaneous vaginal delivery rate was high, with a caesarean delivery rate and instrumental delivery lower than 16% and 15%, respectively. The limitations of this study include (i) its retrospective design, (ii) the limited accuracy of ultrasound determinations of fetal weight, particularly at the extremes of weight, and (iii) the assumption that the weight percentile differ-

ence between delivery and 35-week gestation ultrasound is equivalent to the difference between the weight percentile of a ultrasound near delivery and the 35-week gestation ultrasound.

Conclusions

We demonstrated that fetuses with normal weight at 35 weeks who display decreased percentile weight between 35 weeks of gestation and birth have a greater prevalence of APOs. Although the differences are significant with any amount of percentile decrease, the RR is greater when the decrease is ≥40 percentiles and doubles the RR with respect to the normal population. However, the percentile difference between the 35th week of gestation and birth alone has poor discrimination ability to detect APOs.

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Statement of Ethics

This study protocol was reviewed and approved by The Clinical Research Ethics Committee of Aragon, Approval No. PI 18/333. Due to the nature of this retrospective study, obtaining written patient consent was not necessary nor who approved or mentioned that this is included in the mentioned approval of the ethics committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.D.P. and M.T.-D. contributed to the conception of the study. P.D.P, M.T.-D., R.S.-C., L.M.E., S.C.-M., G.S., and F.R.P.-L. contributed to the design of the work. P.D.P., R.S.-C., L.M.E., and M.T.-D. carried out data acquisition. P.D.P. and L.M.E. performed statistical analysis. All authors were involved in the interpretation of the study results, as well as the drafting and revision of the manuscript, and all approved the final version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Article

Personalized Model to Predict Small for Gestational Age at Delivery Using Fetal Biometrics, Maternal Characteristics, and Pregnancy Biomarkers: A Retrospective Cohort Study of Births Assisted at a Spanish Hospital

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Abstract: Small for gestational age (SGA) is defined as a newborn with a birth weight for gestational age < 10th percentile. Routine third-trimester ultrasound screening for fetal growth assessment has detection rates (DR) from 50 to 80%. For this reason, the addition of other markers is being studied, such as maternal characteristics, biochemical values, and biophysical models, in order to create personalized combinations that can increase the predictive capacity of the ultrasound. With this purpose, this retrospective cohort study of 12,912 cases aims to compare the potential value of third-trimester screening, based on estimated weight percentile (EPW), by universal ultrasound at 35–37 weeks of gestation, with a combined model integrating maternal characteristics and biochemical markers (PAPP-A and β-HCG) for the prediction of SGA newborns. We observed that DR improved from 58.9% with the EW alone to 63.5% with the predictive model. Moreover, the AUC for the multivariate model was 0.882 (0.873–0.891 95% C.I.), showing a statistically significant difference with EPW alone (AUC 0.864 (95% C.I.: 0.854–0.873)). Although the improvements were modest, contingent detection models appear to be more sensitive than third-trimester ultrasound alone at predicting SGA at delivery.

Keywords: small for gestational age; estimated percentile weight; combined prediction model; fetal biometry; third trimester ultrasound; pregnancy biomarkers

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1. Introduction

Fetal growth restriction (FGR) is defined as a failure to achieve the endorsed growth potential. This definition includes the so-called true FGR, which associates alterations in the Doppler study, suggesting a hemodynamic redistribution that reflects fetal adaptation to malnutrition/hypoxia, as well as histological and biochemical signs of placental disease with an increased risk of preeclampsia [1]. These fetuses have a 5- to 10-fold increased risk of death in utero and increased risk of perinatal morbidity and mortality and suboptimal long-term outcomes [2–5]. This group also includes fetuses who were referred to as small for gestational age, whose estimated fetal weight (EFW) was below a certain threshold, most commonly the 10th percentile [6,7]. They also have a higher morbidity and perinatal mortality but are not usually associated with the Doppler signs described for FGR. Finally,

a subgroup of the above corresponds to so-called "constitutionally small" fetuses, which are born small, with an estimated percentile weight (EPW) below the 10th percentile, but are otherwise healthy [8].

While these definitions seem conceptually simple, the distinction in clinical practice can be challenging. Most small for gestational age (SGA) babies go unnoticed until birth, even when a routine third-trimester ultrasound is performed [9,10]. On the other hand, this category misses cases of growth restriction that do not fall below the 10th percentile. In spite of this, this definition can still help to identify a subset of pregnancies considered as high risk [1].

Nowadays, the diagnostic strategy for the detection of these fetuses prenatally is routine third-trimester ultrasound, performed around 35–37 weeks of gestation, which evaluates fetal growth. However, this has quite low detection rates (DR), ranging from 50% to 80% [11], and the impact of this on perinatal outcome is unclear [12].

For this reason, the addition of other markers, such as maternal characteristics and biochemical and biophysical parameters, is being studied. Hence, combined models are being designed that either increase the predictive capacity of basic ultrasound in the third trimester of pregnancy to predict SGA or select patients at risk of giving birth to late-onset SGA fetuses [12–18]. In some of these studies, an ultrasound is performed well before delivery (week 30–34) [12,15,19]; in others, several ultrasounds are performed throughout the third trimester of pregnancy, in order to longitudinally assess fetal growth [20]. In others, the Doppler study or circulating biochemical markers, such as serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFLT), are introduced, thus increasing the sensitivity and specificity, as well as the detection rates, of SGA fetuses. However, the above strategies are not routinely performed in low-risk pregnancies [5,13,18,19,21–24].

Recent evidence suggests that the pathologies underlying FGR and SGA take place in the first trimester. An earlier assessment, before the establishment of placental dysfunction, may have the potential to improve treatment and prognosis in clinical practice [25]. The cost effectiveness would be even greater if this identification could be a spinoff from the widely-implemented first trimester combined ultrasound and biochemical screening program for Down's syndrome, which tests for maternal serological markers pregnancy-associated plasma protein A (PAPP-A) and the beta subunit of human chorionic gonadotrophin (β-hCG) [26].

Some studies have already evaluated the individual capacity of PAPP-A and β-hCG to predict SGA. They found that these markers have an independent influence on the final birth weight and correlated a lower PAPP-A with a higher risk of the fetus developing SGA. However, their predictive powers are insufficient for them to be used alone for SGA detection [27–30].

The objective of our study was to compare the predictive capacity for SGA neonates of fetal biometry, performed in the third-trimester ultrasound on all pregnant women in a Spanish hospital between 35 and 37 weeks of gestation, with a multivariate model composed of the aforementioned ultrasound, plus maternal characteristics and biochemical markers used for the screening of chromosomal abnormalities in the first trimester of gestation (PAPP-A and β-HCG), tests which are performed in all low-risk pregnant women.

2. Material and Methods

2.1. Study Design

This was a retrospective cohort study of births assisted at the Miguel Servet University Hospital (MSUH), Zaragoza, Spain, between March 2012 and December 2018. The inclusion criteria were as follows: live singleton pregnancies, controlled at the MSUH from the first trimester of gestation; fetal ultrasound assessment at a gestational age of 35 weeks (range 34–36); and deliveries between 37 and 42 weeks of gestational age, with fetuses without stillbirth associated with malformations or chromosomal abnormalities. Of the 16,361 deliveries assisted in our hospital in the study period, only the 12,912 cases that fulfilled the inclusion criteria, such as data availability to estimate percentile weights by

standards, were considered. The selected sample of study participants is described, in detail, in Figure 1.

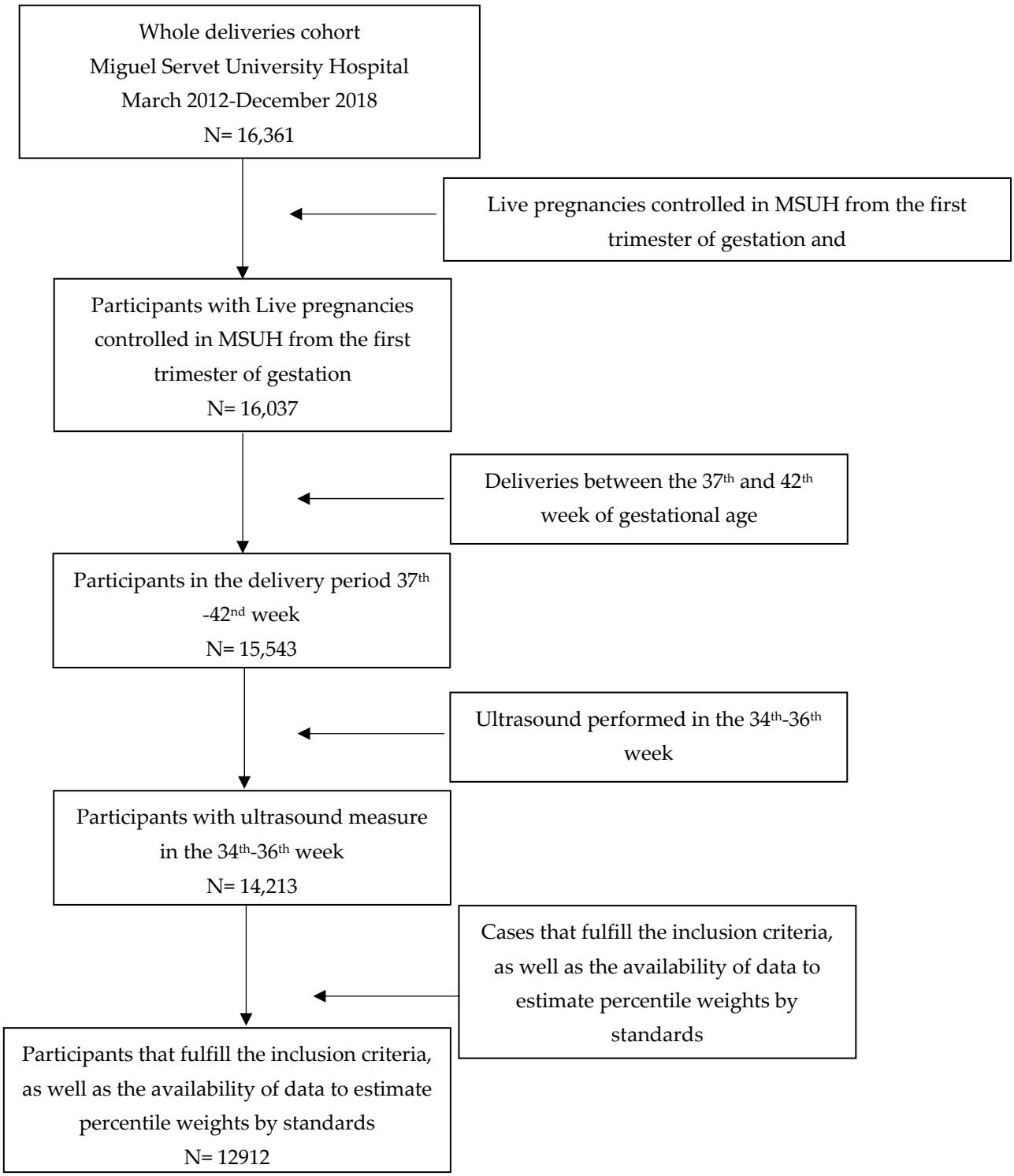

Figure 1. Study participants selection sample.

The last menstrual period was adjusted by the first trimester ultrasound [31]. Universal ultrasound screening was performed at 35 weeks (range 34–36 weeks) at the Ultrasound and Prenatal Diagnosis Unit, using either an ultrasound machine Voluson 730 Expert, E6, E8 (General Electric, Healthcare, Zipf, Austria) or Aloka Prosound SSD-5000 (Hitachi Aloka Medical Systems, Tokyo, Japan). This ultrasound test is routinely performed in all

pregnancies at our center, in an attempt to increase the detection of fetal growth alterations. EFW was calculated with the formula of Hadlock et al. [32], which combines biparietal diameter, cephalic and abdominal circumference (AC), and femur length.

2.2. Estimated Percentile Weight

EPWs were calculated according to the local MSUH standard, customized to fetal gender, built using a modified version of Hadlock et al. growth charts [33], and adjusted to our population, with a coefficient of variation that changes with gestational age [34]. To assess ultrasound weight measures in the third trimester, EPWs were estimated between 34 and 36 weeks of gestational age. As a gold standard for the analysis, SGA was defined as percentile birth weight under 10, using a growth reference for the Spanish population, based on 9362 birth weights [35].

2.3. Estimated Abdominal Circumference Percentile

The AC percentile was estimated according to the Smulian et al. methodology [36]. These authors have derived a formula, based on 10,070 fetuses, for calculating the mean and standard deviation, depending on gestational age. Then, assuming a normal distribution for AC measures at a gestational age, the percentiles were estimated.

2.4. Statistical Analysis

Data were descriptively analyzed using the medians and interquartile ranges for continuous variables and absolute and relative frequencies for categorical variables. Differences between SGA and non-SGA groups were tested using Mann–Whitney and chi-square tests, as appropriate.

The predictive ability of EPW, provided by the MSUH standard, to predict SGAs was analyzed using the area under the receiver operating characteristic curve (AUC) [37]. This area is equivalent to the probability that, given two individuals, one SGA and the other non-SGA, the marker assigns a greater probability of being SGA to the individual that is really SGA. The area ranges from 0.5 to 1, with the 0.5 value corresponding to a random model, 0.7 to an acceptable model, 0.8 to a good model, 0.9 excellent model, and 1 to perfect discrimination.

To improve the prediction of SGA, we explored the added predictive ability of maternal–fetal characteristics and pathologies. These corresponded to: maternal age and body mass index at the start of pregnancy, maternal height, parity, previous cesarean, in vitro fertilization, infant gender, PAPP-A, β-HCG, smoking habits, hypertension, and diabetes. In addition, the AC percentile, estimated at the 35th week of gestational age, was added as a complementary predictor of the EPW to identify SGA fetuses at birth.

AUCs were compared using a bootstrap test [38], and the best model was taken as the one with the largest AUC value. Calibration and clinical utility analysis, by means of a calibration curve [39] and clinical utility curve (CUC) [40], complemented the validation process of the predictive model derived.

Calibration graphically analyzes the concordance between the predictions and real occurrence of the outcome, usually through calibration curves and two informative parameters: 'intercept' (calibration-in-the-large), which measures the difference between average predictions and average outcome; and 'slope', which reflects the average effect of predictions on the outcome.

The CUC reflects the consequences of choosing a cutoff point, in terms of patients with a wrongly classified outcome of interest versus processes avoided. In this curve, the X axis corresponds to the possible threshold probability points, and the Y axis represents the percentage of two measures; the first corresponds to the percentage of missing positive cases below the selected cut-off (FN), and the second to the number of individuals below the cut-off.

Analyses were performed using the R version 4.0.3 language programming package (The R Foundation for Statistical Computing, Vienna, Austria) [41].

3. Results

3.1. Descriptive Results

Table 1 shows the descriptive characteristics of the pregnancies for the SGA and non-SGA groups. For the standard calculation of EFWs, by ultrasound alone at 35 weeks (range 34 + 0 to 36 + 6 weeks), an EPW value < 10 detects 42.1% SGA at birth. The remaining 57.9% correspond to EPW > 10 at the 35th week of gestational age. An AC percentile of <10 at 35 weeks detects only 18.5% of SGA at birth. The variables body mass index, maternal height, parity, number of previous cesareans, in vitro fertilization, maternal smoking habits, hypertension, PAPP-A, and β-HCG all showed statistically significant differences between SGA and non-SGA groups.

Table 1. Maternal baseline characteristics (top), pregnancy (middle), and perinatal characteristics (bottom) of pregnancies. Data are reported as *n* (%) or medians (interquartile range). MSUH, Miguel Servet University Hospital.

Clinical Characteristics	Pregnancies SGA (*n* = 1281)	Pregnancies Non-SGA (*n* = 11,631)	*p*-Value
Maternal characteristics			
Maternal age (years)	33.4 (29.9–36.4)	33.2 (30.0–36.1)	0.299
Maternal body mass index (kg/m^2)	22.5 (20.7–25.4)	23.4 (21.2–26.4)	<0.001
Maternal height (cm)	161 (157–165)	163 (160–168)	<0.001
Parity			
0	872 (68.1%)	6151 (52.9%)	<0.001
1	339 (26.5%)	4411 (37.9%)	
≥2	70 (5.4%)	1069 (9.2%)	
Previous cesarean			
0	1211 (94.5%)	10,739 (92.3%)	0.004
1	69 (5.4%)	826 (7.1%)	
≥2	1 (0.1%)	66 (0.6%)	
In vitro fertilization			
No	1217 (95.0)	11,121 (95.6%)	0.394
Yes	64 (5.0%)	510 (4.4%)	
Maternal smoking habits			
Yes	352 (27.5%)	1676 (14.4%)	<0.001
No	929 (72.5%)	9955 (85.6%)	
Hypertension			
No	1235 (96.4%)	11,485 (98.7%)	<0.001
Chronic	5 (0.4%)	25 (0.2%)	
Preeclampsia	18 (1.4%)	47 (0.4%)	
Gestational	23 (1.8%)	74 (0.6%)	
Diabetes			
No	1126 (87.9%)	10,356 (89.0%)	0.343
Pregestational	6 (0.5%)	81 (0.7%)	
Gestational	132 (10.3%)	1043 (9.0%)	
Carbohydrate intolerance	17 (1.3%)	151 (1.3%)	
Ultrasound parameters at 35 (34–36) weeks			
Gestational age (weeks) at ultrasound	35.1 (35.0–35.3)	35.1 (35.0–35.3)	0.345
Estimated fetal weight (grams) by Hadlock	2186 (2042–2349)	2532 (2362–2715)	<0.001
Abdominal fetal circumference (cm)	293 (284–301)	311 (302–321)	<0.001
Percentile weight by MSUH standard			
<10	513 (42.1%)	542 (4.7%)	<0.001
≥10	768 (57.9%)	11,089 (95.3%)	
Percentile AC by Smulian standard			
<10	237 (18.5%)	200 (17.6%)	<0.001
≥10	1044 (81.5%)	11,431 (82.4%)	

Table 1. *Cont.*

Clinical Characteristics	Pregnancies SGA (*n* = 1281)	Pregnancies Non-SGA (*n* = 11,631)	*p*-Value
Pregnancy and perinatal outcomes			
PAPP-A	0.84 (0.57–1.25)	0.99 (0.68–1.42)	<0.001
β-HCG	0.91 (0.61–1.42)	1.00 (0.67–1.51)	<0.001
Gestational age at delivery	39.6 (38.7–40.4)	40.7 (40.0–41.3)	<0.001
Newborn gender			
Female	663 (51.8%)	5617 (48.3%)	0.020
Male	618 (48.2%)	6014 (51.7%)	
Birth weight	2650 (2480–2760)	3350 (3100–3610)	<0.001

3.2. Small for Gestational Age Prediction

We explored EPW as a predictor of SGA using a logistic regression model, with EPW adjusted for restricted cubic splines with four knots. The AUC was 0.864 (0.854–0.873 95% C.I.), showing a good discriminative ability.

Moreover, we constructed a multivariate model by adding maternal–fetal characteristics and AC percentiles. Table 2 shows the hazard ratio, 95% CI, and *p*-values for significant variables.

Table 2. Multivariate logistic regression model.

Variable	Odds Ratio (95% C.I.)	*p*-Value
rcs (EPW)	0.937 (0.928–0.947)	<0.001
rcs (EPW)′	1.067 (1.030–1.106)	<0.001
rcs (EPW)″	0.813 (0.700–0.942)	0.006
Maternal age	1.050 (1.035–1.065)	<0.001
Maternal height	0.948 (0.937–0.959)	<0.001
Parity	0.639 (0.572–0.711)	<0.001
rcs (PAPP-A)	0.439 (0.031–0.591)	<0.001
rcs (PAPP-A)′	2.211 (1.490–3.066)	<0.001
β-HCG	0.880 (0.806–0.956)	0.004
Hypertension		
Chronic: no	2.887 (0.807–8.665)	0.075
Preeclampsia: no	4.885 (2.443–9.476)	<0.001
Gestational: no	3.854 (2.066–7.009)	<0.001
Smoking habits: no	0.479 (0.408–0.563)	<0.001
Abdominal circumference percentile	0.120 (0.066–0.217)	<0.001

The AUC for the multivariate model was 0.882 (0.873–0.891 95% C.I.), showing a statistically significant difference with the EPW at week 35 (p-value < 0.001), although the increase in AUC was modest. The ROC curves for both models are presented in Figure 2. Regarding the added predictive ability of the AC percentile, a multivariate model without this variable had an AUC value of 0.880, with no significant difference from the full model (p-value = 0.067). Table 3 shows the added predictive ability of each marker, measured by AUC, and discrimination rate for a 10% false-positive rate (FPR).

For the validation process of the EPW at the 35th week and multivariate model to predict SGA, the calibration was explored (Figure 3). Both models showed a good agreement between the predicted probability and actual occurrence, with an intercept of 0 and a slope of 1, corresponding to a perfect calibration.

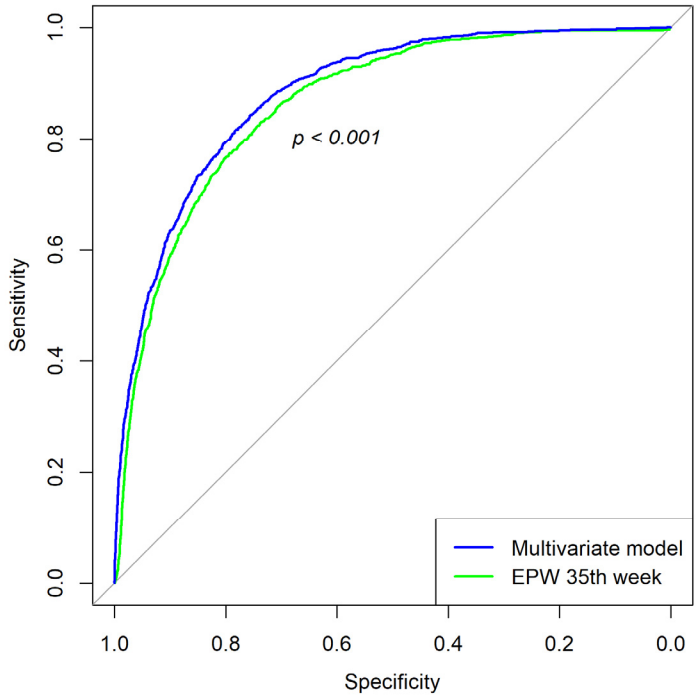

Figure 2. ROC curve for the EPW at 35th week and multivariate model.

Table 3. Screening performance for detection of small for gestational age (SGA) at birth.

Variable	AUC (95% C.I.)	Discrimination Rate (%) at 10% FPR
Abdominal circumference percentile	0.840 (0.829–0.850)	52.3
EPW	0.864 (0.854–0.873)	58.9
+Maternal age	0.865 (0.855–0.874)	59.4
+Maternal height	0.867 (0.859–0.878)	60.1
+Parity	0.873 (0.863–0.882)	60.7
+PAPP-A	0.874 (0.865–0.884)	61.5
+β-HCG	0.875 (0.865–0.884)	61.0
+Hypertension	0.877 (0.868–0.886)	61.8
+Smoking habit	0.880 (0.871–0.889)	61.8
+Abdominal circumference percentile	0.882 (0.873–0.891)	63.5

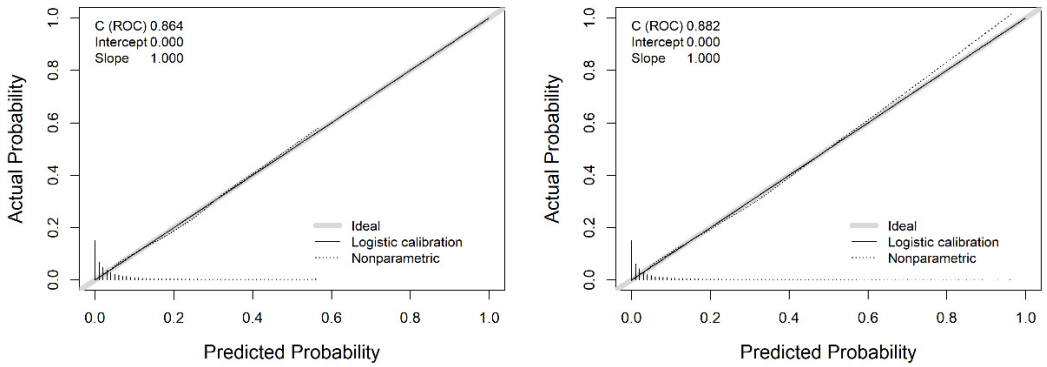

Figure 3. Calibration curve for the EPW at 35th week (left panel) and multivariate model (right panel).

Finally, we analyzed the clinical utility. Figure 4 shows the CUC for EPW at the 35th week (top panel), as well as for the multivariate model (bottom panel).

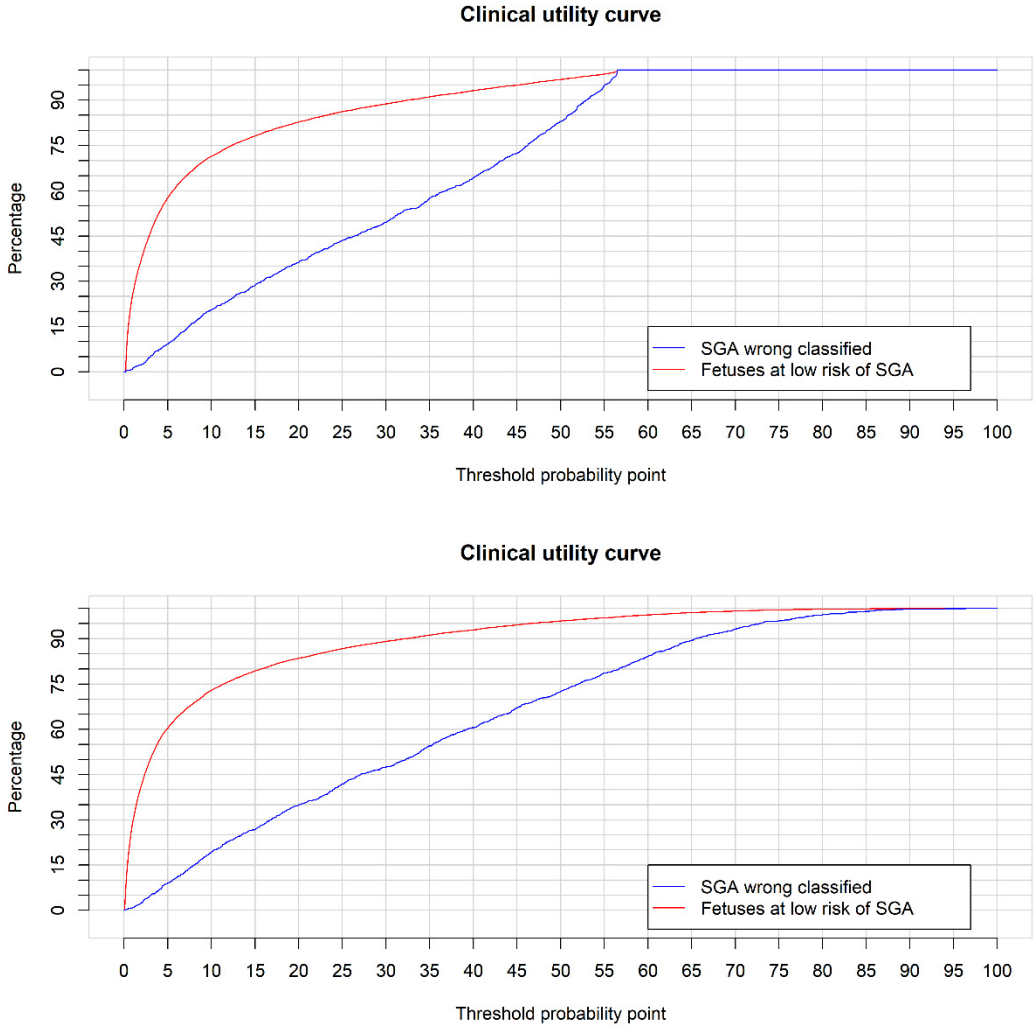

Figure 4. The CUC for EPW at 35th week (top panel) and multivariate model (bottom panel).

The better performance of a marker is reflected in a greater separation of the curves plotted in the CUC. Using the EPW at the 35th week, for a 6% cutoff point in a logistic regression model, 11.5% of SGA would be wrongly classified, with 61.5% of fetuses at low risk of being SGA. For the same cutoff point, in the multivariate model, 10.9% of SGA would be wrongly classified with 63.9% of fetuses at low risk of being SGA. A slightly better performance was, therefore, obtained with the multivariate model.

4. Discussion

Our findings show that a combined screening model, including EPW and AC percentile by ultrasound at the 35th week, maternal characteristics, and biochemical markers, had a better performance than EPW alone in predicting SGA. The combined model presented higher AUC than the model with only EPW. These differences were significant, but the increase was modest. The combined model, without AC percentile, did not show significant differences from the complete model. Moreover, with the combined screening model, 3% fewer fetuses required control for a high risk of SGA.

Our DR improved from 58.9% (threshold EPW 18.2%) using EPW, or from 52.3% with the AC percentile alone (threshold percentile AC 24.9%) to 63.5% using the predictive model, for a 10% FPR. However, this improvement is limited and comparable to the findings of other studies predicting neonates with a birth weight < 10th centile at, or after, term using combined models. These report DRs between 51% and 74%, at a 10% FPR [16,17,42,43], although the markers used in the predictive models are different. In addition, we used

cut-off points higher than the 10th percentile, as a cut-off point of 10 was insufficient, in line with other publications [8,44].

The biochemical markers used in our study, β-hCG and PAPP-A, are routinely tested in the first trimester of pregnancy to screen for chromosomal disorders, and their correlations with chromosomal disorders are already known. Hence, PAPP-A is an independent factor influencing final birth weight, and the lower the PAPP-A, the higher the risk of a fetus developing SGA. However, their predictive powers are not sufficient for them to be used alone for SGA detection [27–30]. Moreover, a significant positive correlation has not been found between birth weight and free β-hCG levels [30]. These results are consistent with our findings of lower PAPP-A and β-hCG values in the group of SGA fetuses than in the group of non-SGA fetuses, both with significant differences.

With regards to combined SGA prediction models, a few studies have examined the performance of screening for SGA at 35–37 weeks' gestation by combining EFW and different markers. One study of 5121 pregnancies reported that, in screening by maternal factors and EFW, the DR of SGA < 10th percentile delivering at >37 weeks was 66%, at a 10% screen-positive rate, and this did not improve with addition of the artery pulsatility index (UtA-PI) and mean arterial pressure [18]. Similarly, a study of 946 pregnancies reported that screening by EFW predicted 59% of SGA < 10th percentile, at a 10% screen-positive rate, and the performance was not improved, either by the addition of UtA-PI or the cerebroplacental ratio [45]. In yet another study of 3859 pregnancies, screened by maternal factors and EFW, the DR of SGA < 10th percentile delivering at >37 weeks was not improved by the addition of PlGF and sFLT [46].

On the other hand, Miranda et al. 2017 used a combined screening model, including a priori risk (maternal characteristics), third trimester (32 + 0 to 36 + 6) EPW, UtA-PI, PlGF, and estriol (with lipocalin-2 for SGA), and achieved a DR of 61% (AUC, 0.86 (95% confidence interval CI, 0.83–0.89)) for SGA cases and 77% (AUC, 0.92 (95% CI, 0.88–0.95)) for FGR. The combined model performed significantly better than using EPW alone ($p < 0.001$ and $p = 0.002$, respectively) [21]. Despite using different biomarkers and not adding Doppler ultrasound, our SGA DRs in the combined model were 63.5% (AUC 0.882 0.873–0.891 95% C.I.).

In their combined model, Souka et al. 2012 used AC, EFW, UA Doppler, smoking status, and first-trimester indices (free β-hCG and PAPP-A multiples of the median) and obtained an AUC = 0.88 for the prediction of SGA, a marginal improvement on EPW or AC alone, but without statistically significant differences [13]. The results of our work were very similar, without the use of AU Doppler, which is not routinely performed when the EFW is above the 10th percentile.

Ciobanu et al. reported a positive DR of 32% (95% CI, 30–36%) in the detection by maternal factors, 66% (95% CI, 63–69%) by maternal factors and EFW at 35–36 weeks of gestation, and 69% (95% CI, 66–72%) with the addition of biomarkers (UtA-PI, umbilical artery pulsatility index, middle cerebral artery pulsatility index, PlGF, and sFLT) [5]. In our cohort, these values were 26.3% (95% CI 23.9–28.8%) with maternal factors alone, 62.1% (95% CI 59.4–64.7%) with the addition of EPW, and 62.4% (95% CI 59.7–64.0%) with the complete combined model.

The strengths of our screening model are its simplicity and affordability, as it includes the standard tests used in screening for chromosomal abnormalities in the first trimester. It is based on variables easily obtained in the routine control of normal pregnancy, without requiring additional tests or parameters to elaborate the predictive model, such as Doppler studies or angiogenic biomarkers.

Several studies have shown that the performance of screening for SGA using a combined model of maternal characteristics and medical history (maternal factors), EFW, and biophysical and biochemical markers is acceptably high for a preterm birth, but disappointingly low for delivery at term [15,42]. Both in our study and in most of those cited here, the contribution of a model that combines maternal characteristics and medical history (maternal factors), EFW, and biophysical and biochemical markers increases the predictive

capacity of SGA fetuses, but only to a small degree. However, other studies have shown this to be acceptably high for mothers who give birth prematurely [15,42].

We analyzed the clinical utility of EPW at the 35th week, as well as the predictive model using maternal–fetal characteristics, by means of the CUC. In this curve we showed the percentage of SGA incorrectly classified using a threshold point, as well as the fetuses at low risk of being SGA at birth. For the EPW at week 35, assuming a loss of 10% of fetuses that would be SGA at birth, 59% of fetuses can be considered as low risk. Alternatively, assuming a loss of 20% SGA cases, 71% of fetuses would be at low risk. Using the predictive model, assuming a loss in SGA cases of 10%, 62% would be considered as low risk; with a loss of 20%, a total of a 74% would be at low risk. From these findings, it can be deduced that, with the addition of maternal fetal characteristics, 3% fewer fetuses would require more controlled follow-up.

Detection of SGA at delivery by third-trimester ultrasound, either by EPW or CA, even with models combined with other maternal variables and first-trimester biochemical markers, is limited, and new tools are required to improve this.

5. Conclusions

Contingent screening models appear to be more sensitive than third-trimester ultrasound screening as the sole technique for predicting SGA at delivery. However, these improvements are modest (from 58.9% using EPW or 52.3% with AC percentile alone to 63.5% using the predictive model). AC at 35-week ultrasound does not appear to be superior to EPW or significantly improve on the full model.

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Informed Consent Statement: Patient consent was waived, as data were fully anonymized, due to the retrospective observational nature of the study.

Data Availability Statement: The data analyzed were retrieved from the Miguel Servet University Hospital database.

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4. DISCUSIÓN

En la actualidad, el diagnóstico prenatal del crecimiento fetal anormal y en consecuencia el diagnóstico de eventos perinatales adversos, se basa en la discrepancia entre el peso fetal estimado por ecografía para un feto determinado y el esperado para las semanas de gestación de acuerdo con unos estándares de crecimiento[43] [60]. Como ya hemos comentado, existen múltiples estándares de crecimiento con los que comparar un feto y todavía no hay acuerdo en cuál es mejor usar.

En los tres primeros artículos de los que está formada esta tesis se analiza la capacidad que tienen los estándares de crecimiento más utilizados tanto a nivel nacional como internacional para predecir eventos perinatales adversos y alteraciones en el crecimiento. En el primer artículo nos centramos en la capacidad de detectar RPA en la población global de fetos. El segundo se enfoca más en los fetos GEG y en el tercero en los fetos denominados PEG tardíos.

Los hallazgos principales han sido: con respecto a la población general de fetos, no existen diferencias significativas en cuanto a la capacidad que tiene el PPE para predecir RPA para los distintos estándares de crecimiento. Para detectar fetos GEG es significativamente mayor la capacidad de predicción de los estándares de FMF y el estándar del HUMS no personalizado. Por el contrario, la tasa de detección de RPA en estos fetos es significativamente mayor para los estándares personalizados. La capacidad predictiva de fetos PEG es ligeramente mejor para los estándares no personalizados, al igual que la tasa de detección de RPA en estos fetos.

Dada la falta de acuerdo con respecto a cuál es el mejor estándar a utilizar y la deficiente capacidad de predicción tanto de RPA como de alteraciones en el crecimiento fetal mediante una única ecografía en la semana 35 de gestación, llevamos a cabo dos nuevos trabajos de investigación que evalúan nuevas estrategias diagnósticas que intentan mejorar estas tasas de detección. En el primero de ellos utilizamos la velocidad de crecimiento fetal en el tercer trimestre de gestación, calculada como la diferencia de peso entre dos ecografías desde la semana 35 al parto, para poder valorar si la disminución del crecimiento fetal al final del tercer trimestre de gestación está asociada con la aparición de RPA y si esto serviría como un buen parámetro para predecirlos. En el último utilizamos como estrategia diagnóstica un modelo multivariante en el cual, aparte de la ecografía de la semana 35, se añaden las características maternas y los marcadores

bioquímicos utilizados para el cribado de anomalías cromosómicas en el primer trimestre de gestación (PAPP-A y β-HCG), pruebas que, en nuestro medio, se realizan a todas las gestantes de bajo riesgo. Comparamos la capacidad predictiva de neonatos PEG de este modelo multivariante con respecto al método tradicional de la ecografía de tercer trimestre.

Los hallazgos principales de estos dos trabajos han sido: los fetos con disminución en el percentil de crecimiento entre las 35 semanas de gestación y el nacimiento tienen una mayor frecuencia de RPA. El modelo multivariante diseñado tiene un mejor rendimiento que el PPE solo en la predicción de PEG.

En el primer trabajo, las tasas de detección de RPA totales para todos los estándares en la ecografía de la semana 35, oscilaron entre el 12,7 % con el estándar personalizado del HUMS y el 14,4 % con el estándar no personalizado del HUMS.

Nuestros resultados reportados son similares a los encontrados por Hua et al.[191] en un estudio en el que compararon 3 estándares de crecimiento fetal (INTERGROWTH-21st, Instituto Nacional de Salud Infantil y Desarrollo Humano y estándares de crecimiento fetal de la OMS) concluyendo que todos ellos proporcionaban una precisión limitada para identificar fetos en riesgo de RPA.

Sovio et al.[15] llevaron a cabo un estudio en mujeres nulíparas con fetos PEG a las cuales se les realizaba la ecografía en la semana 26 y 36. Compararon la capacidad predictiva de PPE para la detección de RPA utilizando un estándar personalizado y otro no personalizado y concluyeron que la personalización no aumenta la fuerza de asociación entre PEG y morbilidad neonatal. En el caso de nuestro estudio comparamos los estándares para todos los fetos (PEG y no PEG) con la ecografía que se realiza universalmente a las 35 semanas y únicamente con partos a término y los resultados encontrados fueron similares a los casos PEG, sin ninguna diferencia significativa entre los estándares de crecimiento personalizados y no personalizados.

Con respecto a la predicción de RPA al nacimiento, Sovio et al.[134] informaron que las capacidades diagnósticas tanto de los estándares personalizados como los no personalizados para detectar RPA son deficientes, aunque los recién nacidos PEG estén asociados con el riesgo de estos RPA. En nuestro estudio observamos diferencias

significativas en los valores medianos de peso y PPE al parto entre gestantes sin complicaciones y aquellas que desarrollaron RPA para los 5 estándares analizados. Los resultados fueron independientes de la personalización o no del estándar utilizado, con sensibilidades y valores de AUC para la detección de RPA ligeramente superiores a los de Sovio et al.[134]

Ganzevoort et al. en 2018[192], sugirieron que el uso de la dicotomización en el percentil 10 para definir el crecimiento fetal normal frente al anormal era una limitación para la ecografía como prueba de diagnóstico única para predecir RPA. Según nuestros resultados, aunque un aumento del punto de corte por ecografía mejoraría la tasa de detección de RPA, también aumentaría tanto la TFP como el número de pruebas innecesarias realizadas.

En 2018, Iliodromiti et al.[193] recomendaron aumentar los puntos de corte para la detección de RPA en el momento del parto al percentil 25, ya que el percentil 10 se ha considerado muy restrictivo, independientemente de que el estándar esté personalizado o no. Estos datos son acordes a nuestros resultados, los cuales mostraron que, aunque el PFE en el momento del parto está asociado significativamente con los RPA, el punto umbral del percentil 10 en el momento del parto también es limitado. La capacidad del PFE de predecir RPA aumenta cuando la estimación de la valoración del peso se realiza más cerca del parto.

También encontramos una sobreestimación de PFE por ecografía con el estándar de Figueras et al.[70] y una subestimación con el estándar de la OMS tanto por ecografía a las 35 semanas como en el momento del parto. Sin embargo, sus capacidades predictivas fueron similares a las de otros estándares después de ajustar el umbral del percentil. Observamos que el método para calcular el PFE por el estándar de la OMS podría introducir una falta de calibración en el PFE, pero no representa una pérdida en la capacidad de discriminación. Además, nuestra población puede diferir del estándar de la OMS[64] de manera similar a como se muestra en un estudio de Grantz et al[194].

El modelo de Figueras et al.[70] y del HUMS[72] se desarrollaron siguiendo los estándares de Hadlock et al.[195] aunque en el HUMS se hicieron modificaciones en los coeficientes de variación y modelo de crecimiento exponencial para construir un estándar que pudiera

explicar las diferencias en PFE por ecografía. Es importante resaltar que en el estándar de INTERGROWTH-21st[42] la fórmula utilizada es la de Stirnemann et al.[38], que incluye solo las CC y CA para calcular el PFE, lo que introduciría un sesgo, en contraste con la fórmula de Hadlock et al[37].

En el segundo artículo demostramos la utilidad del PPE calculado por ecografía a las 35 semanas de gestación como predictor de GEG en el parto a término con cualquier modelo estudiado. Al comparar los 6 modelos de crecimiento se observó que tenían una buena capacidad predictiva para detectar GEG, similar para todos ellos.

Si lo que analizamos es la capacidad predictiva de detectar RPA en esos fetos GEG en la ecografía de las 35 semanas de gestación, los estándares personalizados de Figueras y del HUMS son los que muestran una mayor capacidad diagnóstica, con tasas de detección del 12,6 y 12,2%, respectivamente, con diferencias estadísticamente significativas con respecto a los no personalizados. A diferencia del artículo anterior, en el que no se encontró ninguna diferencia significativa entre los estándares personalizados y no personalizados al analizar la capacidad predictiva de PFE para detectar RPA en el conjunto de todos los fetos.

Con respecto a la capacidad de detección en el momento del parto, los estándares no personalizados presentan una mayor capacidad predictiva para detectar GEG, con la excepción del estándar internacional de la OMS, aunque esta capacidad predictiva no fue perfecta para ninguno de los 6 estándares de crecimiento. Varios estudios han informado de una subestimación de PFE en GEG debido al error intrínseco de la ecografía[132], lo que podría, al menos parcialmente, justificar estas tasas de detección.

Sovio et al. en 2018[119] apoyaron la ecografía universal de 36 semanas versus las exploraciones selectivas para detectar recién nacidos GEG, con una mejoría en las tasas de detección del 27 % al 38 %. Su estudio incluyó partos prematuros y una baja tasa de GEG del 4,6 %, lo que podría explicar la TFP más baja de su estudio.

En 2012, Zhang et al[196]. mostraron una mayor capacidad predictiva para los recién nacidos GEG cuando se realiza una ecografía cerca del parto. El estudio de Souka et al. de 2013[23] informaron de una tasa de detección del 53 % por ecografía a las 32-33 semanas, que aumentó al 63 % por ecografía a las 35-36 semanas. Este estudio coincidió con

nuestros resultados, aunque los criterios de inclusión son diferentes (recién nacidos GEG definidos como superiores al percentil 95). Esto probablemente se deba a que el feto tiene menos tiempo para modificar su percentil de peso hasta el nacimiento a medida que disminuye el intervalo de realización de la ecografía y el parto. En la misma línea, un estudio de cohortes longitudinales de Tarca et al. realizado en 2016[197], mostró una tasa de detección del 54 % de los recién nacidos GEG. Una posible razón de sus menores tasas de detección podría estar asociada a que realizaron la ecografía antes de las 34 semanas. Frick et al.[198] también publicaron resultados similares realizando la ecografía a las 30-34 semanas con una tasa de detección del 41,3 %, que aumentó al 48,6 % a las 35-37 semanas. Este trabajo consideró factores maternos y también enfatizó que la capacidad de predecir recién nacidos GEG aumentaba cuando la estimación de la evaluación del peso se realiza más cerca del parto.

En el tercer artículo, todos los estándares de crecimiento utilizados mostraron una buena capacidad predictiva de fetos PEG, similar para todos los modelos, aunque ligeramente mejor para los estándares no personalizados. Los resultados del trabajo confirmaron que un intervalo menor entre la realización de la ecografía y el momento del parto se correlaciona con mejores tasas de detección de nacidos PEG.

En nuestros resultados encontramos una subestimación del percentil 10, por ecografía a las 35 semanas con los modelos de la OMS (7,5%) y la FMF (2,7%), y una sobreestimación con el estándar de Figueras (18,1%); por lo que podemos concluir que estos modelos tienen una falta de calibración para nuestra población de estudio. Los estándares no personalizados del HUMS (11,9%) y personalizado (12,2%) e INTERGROWTH-21st (12,7%) se ajustaron mejor al percentil 10, con un error mínimo, probablemente por la exclusión de partos prematuros.

Cuando analizamos la capacidad predictiva de RPA de los 6 estándares por percentil de peso menor de 10 a la semana 35 de edad gestacional, los modelos personalizados de FMF y el estándar de la OMS mostraron la mayor capacidad diagnóstica (27,0% y 17,4% respectivamente), con diferencias estadísticamente significativas con el resto de modelos. La principal razón de ello radica en la mayor proporción de fetos con PPE menor de 10 para los estándares de la FMF (21,2%) y la OMS (12,6%). En cualquier caso, con proporciones similares de PPE menor de 10, los modelos no personalizados del HUMS e

INTERGROWTH-21 mostraron una mejor capacidad predictiva de RPA que los personalizados.

En comparación con los artículos previos, en el primero no se encontraron diferencias significativas entre los estándares personalizados y no personalizados al analizar la capacidad predictiva de PPE para detectar RPA en el conjunto de la población estudiada; por el contrario, en el segundo al estudiar la capacidad predictiva de RPA en los fetos GEG los estándares personalizados de Figueras y del HUMS son los que muestran una mayor capacidad diagnóstica, con diferencias estadísticamente significativas con respecto a los no personalizados.

No existe un consenso internacional sobre la realización de una ecografía universal en el tercer trimestre; dos guías internacionales, el RCOG[107] y el ACOG[199] no recomiendan la ecografía universal para detectar anomalías en el crecimiento fetal. Sovio et al.[15], sin embargo, encontraron que la ecografía universal del tercer trimestre en mujeres nulíparas, en comparación con ecografías seleccionadas, triplicaba la detección de recién nacidos PEG con percentil menor de 10 y podía identificar fetos con CIR con mayor riesgo de morbilidad neonatal.

El PFE en la ecografía del tercer trimestre a las 32 semanas ha demostrado ser un buen modelo predictivo (AUC mayor de 0,85) para la detección de fetos PEG en el parto en varios estudios, aunque con tasas de detección limitadas para nacimientos PEG de inicio tardío[24,181,200]. Según varios estudios, la tasa de detección de PEG en el momento del parto por ecografía entre las semanas 33 y 34 es de aproximadamente el 52 %, y entre las semanas 36 y 37 es de aproximadamente el 60 % (TFP del 10 %)[45,201,202], por tanto, la detección es mayor cuanto más tarde se realiza la ecografía[16,23,129]. En nuestro trabajo, la capacidad predictiva de PEG en el parto por ecografía a las 35 semanas también es limitada para los 6 modelos de crecimiento y, en general, un intervalo más corto entre la ecografía y el parto se correlacionó con mejores tasas de predicción.

Blue et al., en 2018[203] compararon los modelos de la RCOG y ACOG para la detección de PEG en el parto, con una edad gestacional promedio de parto de 37,7 semanas y ecografías realizados 2 semanas previas al parto y mostraron que ambos modelos tenían una capacidad predictiva moderada (AUC de 0,78 y 0,76, respectivamente). En otro

estudio de Blue et al. en 2019[204], los modelos de Hadlock e INTERGROWTH-21st para la detección de PEG, con partos a las 37 semanas de media y ecografía en las dos semanas previas, mostraron buenas capacidades predictivas (>0,90), con punto de corte de percentil óptimo del 15% para el modelo de Hadlock y del 22% para el de INTERGROWTH-21st. Ambos estudios no son comparables al nuestro ya que aunque muestran mínimas diferencias en la predicción de PEG independientemente del modelo utilizado, ninguno estudió estándares personalizados.

En dos estudios de Odibo et al. en 2018[205] y 2019[206] en los que utilizan la misma muestra, compararon tres modelos de crecimiento diferentes (INTERGROWTH-21st, un modelo personalizado local, y el de Hadlock). Observaron una capacidad predictiva moderada de PEG al parto con cualquiera de ellos (0,67, 0,62 y 0,69, respectivamente). Realizaron ecografías entre la semana 26 y 36+6, y el intervalo medio entre la ecografía y parto fue de 6,7 semanas, también diferente a nuestro trabajo. Reboul et al., en 2017[207] encontraron que los modelos de Hadlock y Gardosi personalizados tenían una capacidad predictiva moderada de PEG en el parto (0,768 y 0,708, respectivamente), con tasas de detección algo más altas para el estándar de Hadlock, aunque con una media de realización de ecografía a las 32 semanas, inferior a la nuestra, lo que podría justificar la menor capacidad predictiva.

En la práctica clínica podemos decir que más importante que la elección del estándar de crecimiento, es su calibración antes del uso clínico, tanto por ecografía como al parto, en la población de referencia. Las características fisiológicas y no patológicas de cada población son las que nos permitirán calibrar el estándar a utilizar. Con los estudios actuales realizados sobre el momento de realización de la ecografía del tercer trimestre y el intervalo ecografia-parto, junto con nuestro estudio comparativo de estándares, podemos afirmar que el momento que mejor predice los casos de PEG es el más próximo al parto; sin embargo, no podemos retrasar la ecografía universalmente a las 37 semanas, ya que no detectaríamos CIR precoces.

De acuerdo con nuestros resultados, sería apropiado elevar el punto de corte del percentil de peso estimado por ecografía por encima de 10 para el control del crecimiento fetal, buscando el equilibrio adecuado con la TFP. Esto se debe a que el percentil 10 se ha mostrado insuficiente y con baja capacidad predictiva de PEG al parto

y, por tanto, fetos que potencialmente pueden ser CIR incluso antes del parto pueden escapar al control y, por tanto, aumentar su morbimortalidad.

En el cuarto artículo utilizamos el concepto de velocidad de crecimiento como método de diagnóstico. Para ello utilizamos el percentil de peso en la ecografía de la semana 35 de gestación y el percentil de peso al nacer, asumiendo que la diferencia de percentiles entre ambos momentos sería un marcador subrogado de lo que realmente se puede medir, que es la diferencia de percentiles entre una ecografía cerca del parto y una ecografía en la semana 35

Los resultados de este estudio demuestran que los fetos con disminución en el percentil de crecimiento entre las 35 semanas de gestación y el nacimiento tienen una mayor frecuencia de RPA. Observamos que los fetos con un potencial de crecimiento reducido al final del tercer trimestre tienen mayor riesgo de RPA, y otros estudios respaldan esta premisa[92].

Deter et al[135]. introdujeron previamente el término evaluación de crecimiento individualizado que establece estándares para cada parámetro anatómico en un feto o neonato (cada individuo es su propio control) e identifica la patología del crecimiento como desviaciones de estos estándares, utilizando un solo parámetro o un conjunto de parámetros. Este enfoque requiere al menos 2 medidas separadas en el tiempo con una diferencia mínima de 2 a 3 semanas[11]. Sovio et al. en 2015[15] y 2018[134] y Deter et al. en 2017[135] informaron que la velocidad de crecimiento fetal o el porcentaje de desviación del crecimiento, independientemente del modelo de población utilizado (universal, local, prescriptiva o descriptiva), es más relevante que PFE por ecografía para determinar trastornos del crecimiento intrauterino[54]. Además, Bligh et al. en 2019[92] sugirieron que algunos fetos exhiben una disminución sutil en la velocidad de crecimiento a término, lo que puede ser responsable del mayor riesgo de compromiso intraparto y RPA. De hecho, en los casos de lactantes, se ha demostrado repetidamente que la velocidad de crecimiento en la primera infancia es un mejor predictor del peso subsiguiente que cualquier otra medida transversal[136]**.** Otros autores han asociado la velocidad de crecimiento fetal del tercer trimestre con la aparición de efectos adversos[15,130,133]. Este hallazgo es consistente con nuestro trabajo, que mostró una mayor frecuencia de RPA en el grupo de fetos con una disminución del percentil de peso desde las 35 semanas de

gestación hasta el nacimiento. Cuando analizamos la tasa de crecimiento en el tercer trimestre de gestación en toda la población en relación con la aparición de RPA, observamos que, a menor tasa de crecimiento, mayor frecuencia de RPA. En nuestro estudio es altamente significativo un descenso mayor de 40 percentiles, lo que podría establecerse como un posible punto de corte para detectar la población en riesgo de RPA. Nuestro RR es aproximadamente el doble que el de la población normal y está en consonancia con los datos de MacDonald et al.[133] Estos autores también demostraron una asociación entre la acidosis neonatal y una disminución de más de 35 percentiles en fetos nacidos con un peso normal.

Se ha recomendado una disminución de más de 2 cuartiles (o más de 50 percentiles) según los criterios de consenso para definir un feto CIR[54].

Por otro lado, Sovio et al. en 2018[134] no lograron encontrar una asociación significativa entre la velocidad de crecimiento lenta de la CA entre el segundo y tercer trimestre y la aparición de resultados adversos (RR 1,36) en una cohorte de mujeres nulíparas no seleccionadas. Esta asociación fue incluso más pequeña cuando se consideraron sólo los recién nacidos con un peso normal. Por el contrario, nosotros observamos diferencias significativas y un mayor RR en el grupo con descenso percentil entre las 35 semanas de gestación y el nacimiento. La disparidad de los dos estudios puede estar relacionada con el período de embarazo analizado debido a las diferencias en la insuficiencia placentaria temprana y tardía.

Encontramos que cualquier disminución del percentil es un factor de riesgo para cada RPA en particular. Nuestros resultados concuerdan con otras publicaciones recientes. Chatzakis et al.[137] mostraron que una desaceleración del crecimiento fetal mayor o igual al percentil 50 en fetos no PEG se asoció con un mayor riesgo de ingreso en la UCI neonatales (OR 1,8) y muerte perinatal (OR 3,8). Pacora et al.[138] encontraron que un feto con una disminución de la velocidad del percentil de más de 50 puntos entre los controles tiene un riesgo 4,7 veces mayor de morir antes del parto.

Cabe destacar que el valor estimado del AUC para la disminución del percentil mostró una pobre capacidad discriminativa y baja tasa de detección de RPA. Esto es concordante con el estudio de Hutcheon et al. de 2010[208] que no pudo observar ningún beneficio del

uso de percentiles de crecimiento condicionales en lugar del PFE para identificar RPA secundarios a la restricción del crecimiento. Esto también fue respaldado por la pequeña contribución de la velocidad de crecimiento al cálculo del PFE a las 35–36 semanas para la predicción de neonatos PEG y RPA observados por Ciobanu et al. en 2019[82]. Al igual que Hiersch et al.[44], quienes en su publicación de 2018 concluyeron que las evaluaciones ecográficas seriadas, ya sea mediante el cálculo de la velocidad de crecimiento fetal, los percentiles condicionales, los métodos basados en proyecciones o la evaluación del crecimiento individual, parecen prometedores para detectar retrasos de crecimiento con mayor riesgo de RPA en embarazos de alto riesgo, sin embargo, en embarazos de bajo riesgo siguen sin estar claros.

En nuestro trabajo analizamos la relación entre el crecimiento fetal y los RPA en varios subgrupos de disminución del percentil entre las 35 semanas de gestación y el nacimiento, encontrando que el grupo de fetos con descenso del percentil mayor de 40 puntos tenía el doble de probabilidades de sufrir RPA, aunque el riesgo no aumentaba linealmente con respecto a la disminución del PPE. En cualquier caso, tal vez hubo otros factores (edad avanzada, fumadores y factores bioquímicos) que podrían estar asociados con una caída del percentil al final del embarazo, y las direcciones de investigación futuras deberían determinar qué fetos por encima del percentil 10 en la ecografía del tercer trimestre se beneficiarían de la repetición ecográfica para detectar aquellos con riesgo de retraso del crecimiento tardío y por tanto con mayor riesgo de RPA. Además, quedan por determinar otros parámetros maternos y fetales, ya que la velocidad de crecimiento fetal por sí sola tiene poca sensibilidad para detectar RPA.

Sobre esta línea de investigación desarrollamos nuestro último trabajo en el que diseñamos un modelo multivariante compuesto por una ecografía en el tercer trimestre de gestacion más las características maternas y marcadores bioquímicos utilizados para el cribado de anomalías cromosómicas en el primer trimestre de gestación (PAPP-A y β-HCG).

Nuestros hallazgos mostraron que un modelo de detección combinado, que incluye PPE y percentil CA por ecografía en la semana 35, características maternas y marcadores bioquímicos, tuvo un mejor rendimiento que el PPE solo en la predicción de PEG. El modelo combinado presentó una AUC más alta que el modelo con solo PPE. Estas

diferencias fueron significativas, pero el aumento fue modesto. El modelo combinado, sin percentil CA, no mostró diferencias significativas con el modelo completo. Además, con el modelo de cribado combinado, un 3 % menos de fetos requirieron control por un alto riesgo de PEG.

Nuestra tasa de detección mejoró del 58,9 % usando únicamente PPE, o del 52,3 % con el percentil CA solo, al 63,5 % usando el modelo predictivo, para una TFP del 10 %. Sin embargo, esta mejora es limitada y comparable con los hallazgos de otros estudios que predicen recién nacidos con un peso al nacer menor del percentil 10 a término o después del término utilizando modelos combinados. Estos estudios reportan tasas de detección entre 51% y 74%, con una TFP del 10% [173,174,181,209], aunque los marcadores usados en los modelos predictivos son diferentes.

Los marcadores bioquímicos utilizados en nuestro estudio, β-hCG y PAPP-A, se realizan de forma rutinaria en el primer trimestre del embarazo para detectar trastornos cromosómicos, y ya se conocen sus correlaciones con los trastornos del crecimiento fetal. Se ha comprobado, además, que PAPP-A es un factor independiente que influye en el peso final al nacer, y cuanto menor sea la PAPP-A, mayor será el riesgo de que un feto se convierta en PEG. Sin embargo, su capacidad predictiva es insuficiente para que se utilice solo para la detección de PEG[169–172]. Con respecto a la β-hCG libre, no se ha encontrado una correlación positiva significativa entre el peso al nacer y los niveles de la misma[172]. Estos resultados son consistentes con nuestros hallazgos de valores más bajos de PAPP-A y β-hCG en el grupo de fetos PEG que en el grupo de fetos no PEG, ambos con diferencias significativas.

Con respecto a los modelos de predicción de PEG combinados, algunos estudios han examinado el rendimiento de la detección de PEG a las 35–37 semanas de gestación mediante la combinación de PFE y diferentes marcadores. Un estudio de 5121 embarazos informó que, la tasa de detección de fetos PEG con percentil menor de 10 y con parto por encima de las 37 semanas mediante la combinación de factores maternos y PFE, fue del 66 %, con una TFP del 10 %, y esto no mejoró con la adición del índice de pulsatilidad arterial (UtA-PI) y presión arterial media[24]. De manera similar, un estudio de 946 embarazos informó que el cribado mediante PFE predijo un 59 % de PEG con percentil menor de 10, con una TFP del 10 %, y el rendimiento no mejoró, ni con la adición de UtA-

PI ni con el índice cerebro-placentario[200]. En otro estudio de 3859 embarazos, la tasa de detección de PEG menor de percentil 10 con parto por encima de las 37 semanas mediante factores maternos y PFE no mejoró con la adición de PlGF y sFLT[210].

Por otro lado, Miranda et al. 2017 utilizó un modelo combinado, incluyendo riesgo a priori (características maternas), el cálculo de PPE en el tercer trimestre (32 + 0 a 36 + 6), UtA-PI, PlGF y estriol (con lipocalina-2 para PEG), y logró una tasa de detección del 61 % (AUC 0,86) para casos de PEG y del 77 % (AUC 0,92) para CIR. El modelo combinado se desempeñó significativamente mejor que el uso de PPE solo ($p < 0,001$ y $p = 0,002$, respectivamente)[175]. A pesar de usar diferentes biomarcadores y no agregar ultrasonido Doppler, nuestras tasas de detección de PEG en el modelo combinado fueron 63.5 % (AUC 0.882).

En su modelo combinado, Souka et al. 2012 utilizaron CA, PFE, AU Doppler, tabaquismo e índices del primer trimestre (múltiplos de la mediana de β-hCG libre y PAPP-A) y obtuvo un AUC = 0,88 para la predicción de PEG, una mejora marginal con PPE o CA solo, pero sin diferencias estadísticamente significativas[18]. Los resultados de nuestro trabajo fueron muy similares, sin el uso de AU Doppler, que no se realiza de forma rutinaria cuando el PFE está por encima del percentil 10.

Ciobanu et al. reportaron una tasas de detección de PEG del 32% mediante factores maternos, 66% por factores maternos y PFE a las 35-36 semanas de gestación, y 69 % con la adición de biomarcadores (IP AUt, índice de pulsatilidad de arteria umbilical, índice de pulsatilidad de la arteria cerebral media, PlGF y sFLT)[82]. En nuestra cohorte, estos valores fueron del 26,3 % con factores maternos solos, del 62,1 % con la adición de PPE y del 62,4 % con el modelo combinado completo.

Varios estudios han demostrado que el rendimiento de la detección de PEG utilizando un modelo combinado de características maternas e historial médico (factores maternos), PFE y marcadores biofísicos y bioquímicos es aceptablemente alto para un parto prematuro, pero decepcionantemente bajo para un parto a término[22,209]. Tanto en nuestro estudio como en la mayoría de los aquí citados, la aportación de un modelo que combina características maternas e historia médica (factores maternos), PFE y

marcadores biofísicos y bioquímicos aumenta la capacidad predictiva de los fetos PEG, pero solo en pequeña medida.

5. FORTALEZAS Y LIMITACIONES

Nuestra investigación presenta un tamaño muestral importante, lo cual es relevante ya que debido a la baja prevalencia de RPA se necesita un gran número de pacientes. Hasta donde sabemos, esta es la primera vez que se estudian los PFE con 2 fórmulas de cálculo diferentes, la de Hadlock[37] y Stirnemann et al[38]. Dado que la fórmula de Hadlock et al.[37] sobrestima el PFE con el estándar INTERGROWTH-21st, la fórmula de Stirnemann et al.[38] puede ser recomendable para calcular PFE utilizando este estándar.

Los puntos fuertes de nuestro modelo de detección son su simplicidad y asequibilidad, ya que incluye las pruebas estándar utilizadas en la detección de anomalías cromosómicas en el primer trimestre. Se basa en variables de fácil obtención en el control rutinario del embarazo normal, sin necesidad de pruebas o parámetros adicionales para elaborar el modelo predictivo, como estudios Doppler o biomarcadores angiogénicos.

Las mediciones de la ecografía se realizaron en la práctica clínica habitual; por lo tanto, las estimaciones de peso estaban más concentradas en semanas específicas de edad gestacional. Este estudio además refleja la población de mujeres a término en nuestra institución y sugiere que nuestros hallazgos pueden ser aplicables y relevante para otros entornos sanitarios similares.

La tasa general de parto vaginal espontáneo fue alta, con una tasa de parto por cesárea y parto instrumental inferior al 16 % y al 15 %, respectivamente. Sin embargo, al provenir los datos de un solo hospital y ser de naturaleza retrospectiva podría limitar la generalización de nuestros modelos. La información de la ecografía estaba a disposición de los obstetras, lo que podría significar un sesgo en el manejo de los embarazos. Un pequeño porcentaje de partos son inducciones o cesáreas programadas por CIR, y podrían actuar como factores de confusión en el estudio. Asimismo, no se han tenido en cuenta otros supuestos de finalización anticipada por otras causas.

6. CONCLUSIONES

1. La capacidad del percentil de peso estimado para predecir resultados perinatales adversos es similar, y limitada, tanto para el peso fetal estimado en la ecografía de las 35 semanas como para el momento del parto a término, para todos los modelos de crecimiento estudiados, sin diferencias significativas entre los personalizados y los no personalizados.
2. La utilización del percentil 10 como punto de umbral para el peso fetal estimado por ecografía en la semana 35 de edad gestacional es insuficiente para la predicción de resultados perinatales adversos.
3. Los 6 modelos de crecimiento estudiados muestran una buena capacidad predictiva para la detección de nacidos grandes para su edad gestacional, siendo más eficaces los modelos no personalizados. Sin embargo, los modelos personalizados muestran ventaja en la detección de efectos perinatales adversos asociados a los nacidos grandes para su edad gestacional.
4. Los modelos no personalizados también son más eficaces en la detección de nacidos pequeños para su edad gestacional y en la predicción de efectos perinatales adversos en esta población. A menor intervalo entre la ecografía y el parto mejores tasas de detección de nacidos pequeños para su edad gestacional.
5. La disminución de percentil de peso detectada entre la ecografía de la semana 35 y el nacimiento se asocia con una mayor prevalencia de resultados perinatales adversos.
6. El riesgo relativo de resultados perinatales adversos se duplica cuando el descenso de percentil entre la ecografía de la semana 35 y el nacimiento es mayor o igual a 40 puntos
7. La diferencia de percentiles por sí sola, entre la semana 35 de gestación y el nacimiento, tiene una pobre capacidad de discriminación para detectar resultados perinatales adversos.
8. Los modelos de detección contingente son más sensibles que la ecografía del tercer trimestre como única técnica para predecir nacidos pequeños para su edad gestacional.

7. APÉNDICE

7.1. Criterios de calidad de las publicaciones

En este anexo se muestran el factor de impacto, la categoría y el ranking de la revista en su categoría, en base al factor de impacto de las revistas donde se han publicado los trabajos incluidos en esta tesis doctoral.

Todos los parámetros han sido obtenidos de los informes de citas de revistas disponibles en el sitio web ISI Web of Knowledge y Scimago Journal & Country Rank.

- Revista: Fetal Diagnosis and Therapy.
  Categoría: Obstetricia y Ginecología.
  Factor de impacto JCR: 2.587. Q3 (2020)- 2.208. Q4 (2021).
  Factor impacto SJR: 0,94. Q1 (2020) - 0,94. Q1 (2021)

- Revista: Journal of clinical Medicine.
  Categoría: Medicina.
  Factor de impacto JCR: 4.964. Q2 (2021).
  Factor impacto SJR: 1.04. Q1 (2021).

7.2. Contribución de los autores

Primer trabajo: Savirón-Cornudella R, Esteban L, M, Tajada-Duaso M, Castán-Mateo S, Dieste-Pérez P, Cotaina-Gracia L, Lerma-Puertas D, Sanz G, Pérez-López F, R: Detection of Adverse Perinatal Outcomes at Term Delivery Using Ultrasound Estimated Percentile Weight at 35 Weeks of Gestation: Comparison of Five Fetal Growth Standards. Fetal Diagn Ther 2020;47:104-114. doi: 10.1159/000500453.

Ricardo Saviron Cornudella, Luis Mariano Esteban y Laura Cotaina: concepción del estudio.

Ricardo Saviron, Luis Mariano Esteban, Laura Cotaina, Mauricio Tajada Duaso, Sergio Castán Mateo, Diego Lerma, Gerardo Sanz y Faustino Pérez López: diseño del trabajo.

Ricardo Saviron Cornudella, Laura Cotaina, Diego Lerma y Peña Dieste: adquisición de datos.

Ricardo Saviron Cornudella y Luis Mariano Esteban: análisis estadísticos.

Todos los autores participaron en la interpretación de los resultados del estudio, así como en la redacción y revisión del manuscrito, y todos aprobaron la versión final.

Segundo trabajo: Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, Dieste Pérez P, Pérez-López FR, Castán-Larraz B, Sanz G, Tajada-Duaso M. Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards. Fetal Diagn Ther. 2021;48(1):15-23. doi: 10.1159/000510020.

Ricardo Savirón Cornudella, Luis Mariano Esteban y Rocío Aznar Gimeno: concepción del estudio.

Ricardo Savirón Cornudella, Luis Mariano Esteban, Faustino Pérez López y Mauricio Tajada Duaso: diseño del trabajo.

Peña Dieste Pérez y Mauricio Tajada Duaso: adquisición de datos.

Luis Mariano Esteban, Rocío Aznar Gimeno y Gerardo Sanz: análisis estadísticos.

Todos los autores participaron en la interpretación de los resultados del estudio, así como en la redacción y revisión del manuscrito, y todos aprobaron la versión final.

Tercer trabajo: Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, Dieste-Pérez P, Pérez-López FR, Campillos JM, Castán-Larraz B, Sanz G, Tajada-Duaso M. Prediction of Late-Onset Small for Gestational Age and Fetal Growth Restriction by Fetal Biometry at 35

Weeks and Impact of Ultrasound-Delivery Interval: Comparison of Six Fetal Growth Standards. J Clin Med. 2021 Jul 3;10(13):2984. doi: 10.3390/jcm10132984.

Ricardo Savirón Cornudella, Luis Mariano Esteban y Mauricio Tajada: conceptualización.

Ricardo Savirón Cornudella, Luis Mariano Esteban y Faustino Pérez López: metodología.

Luis Mariano Esteban, Rocío Aznar Gimeno y Gerardo Sanz: software.

Ricardo Savirón Cornudella, Peña Dieste Pérez y Jose Manuel Campillos: validación.

Gerardo Sanz y Jose Manuel Campillos: recursos.

Ricardo Savirón Cornudella, Luis Mariano Esteban, Rocío Aznar Gimeno, Peña Dieste Pérez y Berta Castán Larraz: curación de datos.

Ricardo Savirón Cornudella y Luis Mariano Esteban: escritura del borrador original.

Ricardo Savirón Cornudella y Luis Mariano Esteban: preparación.

Rocío Aznar Gimeno, Peña Dieste, Jose Manuel Campillos, Faustino Pérez López, Berta Castán Larraz, Gerardo Sanz y Mauricio Tajada Duaso: redacción, revisión y edición.

Gerardo Sanz: adquisición de fondos.

Todos los autores han leído y están de acuerdo con la versión publicada del manuscrito.

Cuarto trabajo: Dieste Pérez P, Esteban LM, Savirón-Cornudella R, Pérez-López FR, Castán-Mateo S, Sanz G, Tajada-Duaso M. Reduced Growth in Non-Small for Gestational Age Fetuses from 35 Weeks of Gestation to Birth and Perinatal Outcomes. Fetal Diagn Ther. 2021;48(11-12):768-777. doi: 10.1159/000519639.

Peña Dieste Pérez y Mauricio Tajada Duaso: concepción del estudio.

Peña Dieste Pérez, Mauricio Tajada Duaso, Ricardo Saviron Cornudella, Luis Mariano Esteban, Sergio Castán Mateo y Faustino Pérez López: diseño del trabajo.

Peña Dieste Pérez, Mauricio Tajada Duaso, Ricardo Saviron Cornudella, Luis Mariano Esteban: adquisición de datos.

Peña Dieste Pérez y Mauricio Tajada Duaso: análisis estadístico.

Todos los autores participaron en la interpretación de los resultados del estudio, así como en la redacción y revisión del manuscrito, y todos aprobaron la versión final.

Quinto trabajo: Dieste-Pérez, P.; Savirón-Cornudella, R.; Tajada-Duaso, M.; Pérez-López, F.R.; Castán-Mateo, S.; Sanz, G.; Esteban, L.M. Personalized Model to Predict Small for Gestational Age at Delivery Using Fetal Biometrics, Maternal Characteristics, and Pregnancy Biomarkers: A Retrospective Cohort Study of Births Assisted at a Spanish Hospital. J. Pers. Med. 2022, 12, 762. https://doi.org/10.3390/jpm12050762.

Peña Dieste Pérez, Mauricio Tajada Duaso, Ricardo Saviron Cornudella y Luis Mariano Esteban: conceptualización.

Peña Dieste Pérez, Mauricio Tajada Duaso, Ricardo Saviron Cornudella y Luis Mariano Esteban: metodología.

Luis Mariano Esteban: software.

Peña Dieste Pérez, Mauricio Tajada Duaso, Ricardo Saviron Cornudella y Luis Mariano Esteban: validación.

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Peña Dieste Pérez: investigación.

Sergio Castán Mateo, Gerardo Sanz y Faustino Pérez López: recursos.

Luis Mariano Esteban y Faustino Pérez López: curación de datos.

Peña Dieste Pérez y Mauricio Tajada Duaso: redacción y preparación del borrador original.

Peña Dieste Pérez, Mauricio Tajada Duaso, Ricardo Saviron Cornudella y Luis Mariano Esteban: escritura, revisión y edición.

Ricardo Saviron Cornudella y Faustino Pérez López: visualización.

Sergio Castán Mateo, Gerardo Sanz y Faustino Pérez López: supervisión.

Sergio Castán Mateo y Gerardo Sanz: administración del proyecto.

Gerardo Sanz: adquisición de fondos.

Todos los autores han leído y están de acuerdo con la versión publicada del manuscrito.

7.3 Renuncia de otros coautores

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Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards. Prediction of Late-Onset Small for Gestational Age and Fetal Growth Restriction by Fetal Biometry at 35 Weeks and Impact of Ultrasound–Delivery Interval: Comparison of Six Fetal Growth Standards

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RENUNCIA:

Renuncio a que las publicaciones anteriores puedan ser presentadas como parte de otra tesis doctoral en la modalidad de compendio de publicaciones.

<lugar>,<fecha>

Zaragoza 16 de mayo de 2022

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Programa de doctorado: Medicina

3.- Publicaciones que formarán parte de la tesis y de las que el firmante es coautor
Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards Prediction of Late-Onset Small for Gestational Age and Fetal Growth Restriction by Fetal Biometry at 35 Weeks and Impact of Ultrasound–Delivery Interval: Comparison of Six Fetal Growth Standards

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8. ABREVIATURAS

ACOG: American College of Obstetricians and Gynecologists.

AUC: área bajo la curva.

β-hCG: subunidad beta de gonadotropina coriónica humana.

CA: circunferencia abdominal.

CC: circunferencia cefálica.

CIR: crecimiento intrauterino restringido.

DBP: diámetro biparietal.

FMF: Fetal Medicine Foundation.

GEG: grande para la edad gestacional.

HUMS: Hospital Universitario Miguel Servet.

IC: intervalo de confianza.

IP AUt: índice de pulsatilidad de arteria uterina.

ISUOG: International Society of Ultrasound in Obstetrics and Gynecology.

LF: longitud del fémur.

OMS: Organización Mundial de la Salud.

OR: Odds Ratio.

PAPP-A: proteína plasmática A asociada al embarazo.

PEG: pequeños para la edad gestacional.

PFE: peso fetal estimado.

PlGF: factor de crecimiento placentario.

PPE: percentil peso estimado.

RCOG: Royal College of Obstetricians and Gynaecologists.

RPA: resultados perinatales adversos.

SEGO: Sociedad Española de Ginecología y Obstetricia.

sFlt-1: forma soluble de la tirosina quinasa-1.

TFP: tasa de falsos positivos.

UCI: Unidad de Cuidados Intensivos.

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