

**CERCLAJE CERVICAL EN
SEGUNDO TRIMESTRE EN
GESTANTES CON
INSUFICIENCIA CERVICAL**

TESIS DOCTORAL

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INFORME DE LOS DIRECTORES DE LA TESIS DOCTORAL

El Prof. Alfredo Perales Marín, Doctor en Medicina y Cirugía, Catedrático del departamento de Pediatría, Obstetricia y Ginecología de la Universidad de Valencia, como director de este trabajo; y el Prof. Vicente Serra Serra, Catedrático del departamento de pediatría, obstetricia y ginecología de la Universidad de Valencia, como codirector y tutor de este trabajo;

Certifican que el trabajo de investigación titulado "*Cerclaje cervical en segundo trimestre en gestantes con insuficiencia cervical*" ha sido realizado como compendio de artículos científicos por Diana María Diago Muñoz, estudiante del Programa de Doctorado en Medicina de la Universidad de Valencia y facultativo especialista en el Servicio de Ginecología y Obstetricia del Consorcio Hospital General Universitario de Valencia, bajo su dirección. Dicha memoria reúne los requisitos para su presentación y defensa como tesis doctoral ante el tribunal.

Y para que conste a los efectos oportunos firman la presente certificación en Valencia, a 22 de abril de 2025.

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LISTADO ABREVIATURAS

PP: parto pretérmino

LC: longitud cervical

IC: insuficiencia cervical

IL-6: interleucina-6

IIA: infección intraamniótica

PCR: proteína C reactiva.

LA: líquido amniótico

LDH: enzima lactato deshidrogenasa

AUC: área bajo la curva

Se: sensibilidad

Sp: especificidad

EG: edad gestacional

NS: no significativo

DS: desviación estándar

PPE: parto pretérmino espontáneo

IC: intervalo de confianza

RPM: rotura prematura de membranas

UCIN: unidad de cuidados intensivos neonatales

BCBA: bicorial biamniótico

MCBA: monocorial biamniótico

N/A: información no disponible

LR: razón de verosimilitud

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RESUMEN

Introducción:

El parto pretérmino (PP) afecta al 5-18% de los embarazos y es una de las principales causas de morbilidad y mortalidad neonatal. La medición transvaginal de la longitud cervical (LC) antes de las 24 semanas es el mejor predictor de PP en embarazos únicos y múltiples, independientemente de otros factores de riesgo. El punto de corte para definir un cérvix corto en embarazos únicos y gemelares entre las 18 y 24 semanas es ≤ 25 mm. En gestaciones gemelares, el riesgo de PP antes de las 32 semanas se incrementa 3 veces por debajo de este límite, mientras que una LC por encima de este límite reduce a la mitad el riesgo de PP.

La insuficiencia cervical (IC), es un factor de riesgo para el PP tanto en embarazos únicos como en embarazos múltiples. La definición clásica de insuficiencia cervical es: dilatación recurrente, pasiva e indolora del cuello uterino en el segundo trimestre. La inflamación/infección intraamniótica constituye una causa de insuficiencia cervical, y su presencia es un factor de riesgo para resultados obstétricos adversos.

La realización de una amniocentesis y la determinación de IL-6 intraamniótica antes del cerclaje sigue siendo controvertida, pero varios autores la defienden, ya que el diagnóstico de corioamnionitis subclínica empeora significativamente el resultado obstétrico. No existen estudios previos sobre pacientes con insuficiencia cervical y la determinación vaginal de IL-6. La IL-6 vaginal solo se ha estudiado para la evaluación del parto prematuro sin insuficiencia cervical.

Además, los marcadores inflamatorios en la sangre materna, como la proteína C-reactiva (PCR), están asociados con PP, y se han encontrado niveles elevados de PCR en pacientes con rotura prematura de membranas y con inflamación/infección intraamniótica.

Objetivos:

Primer artículo: Determinar si existe una correlación entre la IL-6 intraamniótica y vaginal en pacientes con insuficiencia cervical en el segundo trimestre de la gestación para poder evitar la realización de una amniocentesis antes del cerclaje indicado por exploración física.

Segundo artículo: Comparar los resultados obstétricos en gestaciones gemelares y únicas diagnosticadas de insuficiencia cervical con un cerclaje indicado por examen físico.

Tercer artículo: Analizar la efectividad del cerclaje en embarazos gemelares con cérvix corto.

Cuarto artículo: Evaluar la utilidad de la IL-6 en la primera bolsa amniótica para descartar inflamación intraamniótica, así como la PCR en sangre materna, para seleccionar a las pacientes con embarazo gemelar que puedan beneficiarse de un cerclaje indicado por exploración física.

Material y métodos:

Primer artículo: Se realizó un estudio de cohortes en el que se incluyeron todas las pacientes con insuficiencia cervical admitidas en el Hospital Universitario y Politécnico La Fe entre 2019 y 2020, y un grupo de control de mujeres asintomáticas en el segundo trimestre de gestación que fueron estudiadas al mismo tiempo. Los criterios de exclusión fueron: contracciones uterinas, corioamnionitis clínica, ruptura prematura de membranas, sangrado activo, dilatación cervical >3 cm, anomalía congénita fetal, muerte fetal y gestación de <18 o >26 semanas. Se incluyeron embarazos únicos y gemelares.

A las pacientes con insuficiencia cervical se les realizó un examen físico, así como una ecografía vaginal y abdominal para medir la dilatación cervical, confirmar la edad gestacional y descartar anomalías congénitas fetales. También se realizaron analíticas de sangre materna y monitorización electrónica fetal. Todas las pacientes se sometieron a una amniocentesis con una aguja del calibre 20 y 15 cm de longitud, y una jeringa de aspiración de 10 ml. Se extrajeron 70 ml de líquido amniótico (LA): 10 ml para análisis microbiológico, 10 ml para análisis bioquímicos (IL-6, leucocitos, glucosa) y otros 50 ml para amnioreducción y se obtuvo una muestra de flujo vaginal para la determinación de IL-6 vaginal. Al grupo control se le realizó ecografía abdominal y vaginal

ambulatoria en el segundo trimestre de embarazo (21 semanas de gestación), y se tomó una muestra de fluido vaginal para la determinación de IL-6.

La inflamación intraamniótica se definió por IL-6 amniótica > 2,6 ng/ml.

La corioamnionitis subclínica se definió por dos o más de los siguientes criterios: glucosa amniótica < 15 mg/dl, leucocitos amnióticos >50/mm³, estearasa leucocitaria amniótica positiva y la enzima lactato deshidrogenasa (LDH) amniótica > 410 U/ml.

La infección intraamniótica se definió por tener un cultivo bacteriano positivo.

Segundo artículo: Se incluyó a todas las mujeres con insuficiencia cervical en el segundo trimestre de embarazo que fueron admitidas en el Hospital Universitario y Politécnico La Fe desde enero de 2009 hasta enero de 2022. Un total de 128 participantes fueron incluidas, 102 embarazos únicos y 26 embarazos gemelares. Todas las pacientes se sometieron a una amniocentesis para descartar inflamación intraamniótica (IL-6 < 2,6 ng/mL). Todas las pacientes con prolapso de membranas a través del orificio cervical externo sin inflamación intraamniótica, corioamnionitis subclínica o clínica fueron candidatas para realizar un cerclaje cervical indicado por exploración física. Aquellas pacientes que rechazaron el procedimiento fueron tratadas con reposo absoluto en cama, 40 mg de heparina de bajo peso molecular subcutánea diaria y antibioterapia intravenosa (1 g de ampicilina cada 6 h y gentamicina 240 mg diarios durante 5 días). Se utilizaron las técnicas de cerclaje de McDonald o Shirodkar según la decisión del cirujano en el momento del procedimiento realizando la misma técnica anteriormente descrita.

Diez profesionales entrenados realizaron el procedimiento. Antes de la cirugía, se administra un supositorio de 100 mg de indometacina, y luego el tratamiento se mantiene durante 48 horas con 25 mg de indometacina cada 8 horas.

Tercer artículo: Estudio de cohorte retrospectivo realizado en dos instituciones universitarias en Valencia (España) con dos protocolos diferentes para el manejo de embarazos gemelares bicoriales biamnióticos asintomáticos con longitud cervical en el segundo trimestre ≤ 25 mm: tratamiento con indometacina, antibióticos y cerclaje (grupo de cerclaje) (N = 43) frente a manejo expectante

(grupo de control) (N = 37). En el grupo de cerclaje, se administró indometacina (oral 50 mg/8h o rectal 100 mg/12h), así como cefuroxima (500 mg/12h) o clindamicina vaginal (100 mg/día) a todas las mujeres durante 2–3 días previos a la colocación del cerclaje. No se realizó amniocentesis en el diagnóstico. Se realizó un cerclaje cervical modificado de Espinosa-Flores por el mismo operador (JF) en todos los casos, utilizando una cinta de Mersilene. Esta técnica permite anclar la sutura a los ligamentos cardinales sin disecar la mucosa vaginal. La técnica de sutura fue modificada por JF para dejar los nudos de la cinta de Mersilene en el labio anterior del cuello. Se administró cefuroxima oral postoperatoria (500 mg/12h) hasta completar 7 días de tratamiento.

Las mujeres en el grupo de control no recibieron indometacina ni antibióticos en el diagnóstico. En su lugar, se realizó una amniocentesis en los casos de barro amniótico y se administró azitromicina oral (1 g/día/5 días) solo cuando se diagnosticó una corioamnionitis subclínica con cualquiera de los siguientes criterios en el líquido amniótico: tinción de Gram positiva, IL-6 > 2,5 ng/ml, leucocitos > 50/mm³, esterasa leucocitaria ≥ 75 o glucosa < 15 mg/dl.

En ambos grupos, se usaron medicamentos tocolíticos, seguidos de progesterona vaginal, cuando se detectaron contracciones uterinas. No se usaron pesarios cervicales.

Cuarto artículo: Estudio retrospectivo y descriptivo realizado en todas las pacientes con embarazo gemelar diagnosticadas de insuficiencia cervical en el segundo trimestre ingresadas en un hospital terciario desde enero de 2012 hasta septiembre de 2023. De acuerdo con el protocolo del hospital, a todas las pacientes se les realizó una ecografía vaginal y abdominal, un análisis de sangre materna y una amniocentesis de la primera bolsa amniótica para descartar IIA, definida por IL-6 ≥ 2,6 ng/dL. Los resultados de los parámetros del líquido amniótico generalmente se informaron aproximadamente en 2 horas, y el cerclaje se realizó dentro de las primeras 24 horas después del diagnóstico. El tipo y la técnica del cerclaje es igual que en los trabajos anteriores (McDonnald y Shirodkar).

Resultados:

Primer artículo: Se incluyeron un total de 20 mujeres en cada grupo. La edad gestacional media en el momento del diagnóstico fue de 22 semanas en las pacientes con insuficiencia cervical y de 21 semanas en el grupo de control. La IL-6 vaginal en el grupo de control (10,875 pg/mL) es mucho más baja que en el grupo de estudio (1308,77 pg/mL). En las pacientes con insuficiencia cervical la expresión de IL-6 vaginal fue más baja que en la cavidad amniótica [promedio de IL-6 en la cavidad amniótica 26890,07 pg/mL, frente a 1308,77 pg/mL en la vagina ($p < 0,01$)]. Mediante el coeficiente de correlación de Spearman [$\rho = 0,709$ ($p < 0,001$)], se encontró una correlación positiva entre los valores de IL-6 amniótica y vaginal. Esta correlación se calculó con la curva ROC, siendo el área bajo la curva 0,929 (IC 95% 0,721–0,995), y el punto de corte 61,4 pg/mL (sensibilidad 83,33%; especificidad 92,86%). Las pacientes con IL-6 vaginal $< 61,4$ pg/mL asociaron un mayor tiempo de latencia entre el diagnóstico y el parto, un mayor peso neonatal y una menor mortalidad perinatal. El cerclaje realizado con IL-6 vaginal $< 61,4$ pg/mL fue el mejor factor predictivo de un buen resultado obstétrico.

Segundo artículo: En comparación con los embarazos únicos, los embarazos gemelares presentaron una prevalencia significativamente mayor de nuliparidad y técnicas de reproducción asistida. La incidencia de inflamación/infección intraamniótica fue similar en ambos grupos (68,62% en embarazos únicos frente a 65,38% en embarazos gemelares). La edad gestacional promedio en el momento del parto sin cerclaje en embarazos únicos fue de 23,83 semanas (IC 95% 22,82–24,84) y en los embarazos gemelares fue de 23,69 semanas (IC 95% 21,8–25,57). La edad gestacional promedio en el momento del parto en las pacientes con cerclaje fue de 37,27 semanas (IC 95% 35,35–39,19) en embarazos únicos y 36 semanas (IC 95% 33,51–38,63) en embarazos gemelares, sin diferencias significativas. El tiempo desde el diagnóstico hasta el parto en las pacientes con IL-6 $< 2,6$ ng/mL fue de 79,88 días, y en las que tuvieron IL-6 $> 2,6$ ng/mL fue de 10,87 días. La edad gestacional al momento del parto fue significativamente mayor en los embarazos únicos y gemelares con cerclaje, en comparación con los que no recibieron cerclaje (log-rank $p < 0,001$).

Tercer artículo: La longitud cervical inicial fue similar en ambos grupos, pero la detección de un cuello corto ocurrió antes en el grupo de cerclaje (21,6 vs 24,1 semanas, $p < 0,001$). Las mujeres con cerclaje tuvieron una mayor latencia del embarazo (12,5 vs 7,7 semanas, $p < 0,001$); mayor edad gestacional en el parto (34,1 vs 31,8 semanas, $p < 0,04$); menor parto pretérmino espontáneo (PPE) < 28 semanas (11,6 % vs 37,8 %, $p < 0,009$); mayor peso al nacimiento (2145 g vs 1733 g, $p < 0,001$); menor peso al nacimiento < 1500 g (12,5 % vs 40,0 %, $p < 0,001$); menos ingresos en la unidad de cuidados intensivos neonatales (UCIN) (24,1 % vs 43,3 %, $p < 0,03$); menor estancia en UCIN (25,6 vs 49,4 días, $p < 0,02$); menor dificultad respiratoria que requirió ventilación mecánica (14,9 % vs 36,5 %, $p < 0,02$); menor persistencia de conducto arterioso (8,9 % vs 26,9 %, $p < 0,008$); y menor resultado adverso neonatal compuesto (26,6 % vs 44,8 %, $p < 0,03$). El cerclaje y la edad gestacional al diagnóstico fueron los únicos predictores independientes de PPE < 32 y < 28 semanas según los análisis multivariantes. Los datos acumulados en la literatura muestran efectos beneficiosos prometedores del cerclaje.

Cuarto artículo: Se incluyeron un total de 28 pacientes con embarazo gemelar e insuficiencia cervical en el segundo trimestre. Entre ellas, 18 pacientes (64,28%) tenían niveles de IL-6 $\geq 2,6$ ng/dL. Se realizó cerclaje en 10 pacientes con IL-6 $< 2,6$ ng/dL. La mortalidad perinatal en los embarazos con IL-6 $\geq 2,6$ ng/dL fue del 77,22%. La edad gestacional en el momento del parto en pacientes con IL-6 $< 2,6$ ng/dL fue de 34 ± 3 semanas, en comparación con 23 ± 4 semanas cuando IL-6 fue $\geq 2,6$ ng/dL ($p < 0,001$). La latencia hasta el parto con IL-6 $< 2,6$ ng/dL fue de $88,1 \pm 31,56$ días, en comparación con $13,11 \pm 20,43$ días cuando IL-6 fue $\geq 2,6$ ng/dL ($p < 0,001$). Se encontraron diferencias significativas en los niveles de PCR en sangre materna entre ambos grupos de estudio (sin IIA $4,32 \pm 3,67$ vs. IIA $13,32 \pm 15,07$, $p < 0,05$). El área bajo la curva de la curva ROC fue de 0,799 (IC 95% 0,596–0,929), con un punto de corte de 3,9 mg/L (S 94,4%, E 62,5%). La edad gestacional en el momento del parto con PCR $< 3,9$ mg/L fue de 33 ± 5 semanas, mientras que en los casos con PCR $\geq 3,9$ mg/L fue de 24 ± 5 semanas ($p < 0,001$). Los días de latencia hasta el parto fueron de $86,5 \pm 44,88$ y $21,95 \pm 30,97$ días ($p < 0,01$), respectivamente. Se obtuvo una correlación

positiva entre los valores de IL-6 de ambas bolsas amnióticas, junto con el coeficiente de correlación de Spearman ($\rho = 0,835$, $p < 0,001$).

Discusiones:

Primer artículo:

Las citoquinas cervicovaginales permanecen estables en embarazos saludables. Esto también se observó en nuestro trabajo, dado que los valores de IL-6 en el grupo control son más bajos que en el grupo de estudio. Una alta concentración de IL-6 vaginal implica un estado inflamatorio activo en el embarazo.

Por lo tanto, si los niveles de IL-6 vaginal están elevados, se debe sospechar inflamación.

El presente estudio prospectivo destaca que el nivel de IL-6 vaginal durante el segundo trimestre de embarazo en pacientes con insuficiencia cervical es más bajo que en el líquido amniótico. Sin embargo, existe una asociación positiva entre IL-6 intraamniótica y vaginal en pacientes con insuficiencia cervical.

Los objetivos secundarios del trabajo son comparar los valores de IL-6 vaginal en mujeres con embarazos de bajo riesgo con gestantes diagnosticadas de insuficiencia cervical durante el segundo trimestre, así como encontrar el mejor punto de corte de IL-6 vaginal que se asocie con un buen pronóstico del embarazo en pacientes con insuficiencia cervical.

La amniocentesis es un procedimiento invasivo que implica un riesgo para el embarazo además de dolor para la paciente. No obstante, su realización antes de la colocación del cerclaje cervical es esencial, dado que la IL-6 intraamniótica constituye un factor pronóstico independiente de éxito o fracaso del cerclaje.

El punto de corte de IL-6 vaginal (IL-6 vaginal $< 61,4$ pg/ml) proporciona el mismo factor pronóstico que la IL-6 amniótica (IL-6 amniótica > 2600 pg/ml) y podría evitar la realización de un procedimiento diagnóstico invasivo antes de la colocación de un cerclaje indicado por exploración física.

Obtener la muestra de IL-6 vaginal es un procedimiento sencillo y no requiere del uso de un espéculo vaginal, lo que podría rasgar la bolsa amniótica e incomodar a la paciente. Además, el nivel de IL-6 vaginal está disponible en un plazo de 90 a 120 minutos.

La expresión de IL-6 vaginal nunca se ha estudiado en la insuficiencia cervical. Sin embargo, se ha analizado para predecir el parto prematuro. Perales et al.

afirman que una baja concentración de IL-6 cervical puede identificar con precisión a mujeres sintomáticas con bajo riesgo de desarrollar un parto prematuro, lo que evita ingresos hospitalarios innecesarios y los efectos secundarios de los tocolíticos y esteroides.

Este estudio preliminar ha proporcionado un punto de corte de IL-6 vaginal (<61,4 pg/ml) en mujeres con insuficiencia cervical, que se asocia con un bajo período de latencia entre el diagnóstico y el parto.

En el trabajo, hay dos pacientes con insuficiencia cervical que tienen un valor bajo de IL-6 vaginal y un valor alto de IL-6 en el líquido amniótico. En la primera paciente se observó un valor de IL-6 vaginal 9,41 pg/ml y de IL-6 intraamniótica 9662 pg/ml, inició periodo activo de parto a los 4 días del diagnóstico, lo que sugiere un falso negativo de IL-6 vaginal.

Los resultados de la segunda paciente fueron: un valor de IL-6 vaginal 3,6 pg/ml e IL-6 intraamniótica 12,686 pg/ml, tuvo un parto 69 días después del diagnóstico de la incompetencia cervical. Esto sugiere un falso positivo de IL-6 amniótica.

Si bien es cierto que la información microbiológica del líquido amniótico no se puede obtener sin una amniocentesis, este estudio revela que la amniocentesis y sus riesgos para el embarazo podrían evitarse antes de la colocación de un cerclaje de emergencia si se determina la IL-6 vaginal.

Existen estudios que evalúan los niveles de IL-6 en suero materno en pacientes con insuficiencia cervical. Park et al. confirman que los niveles plasmáticos elevados de IL-6 predicen moderadamente la infección intraamniótica en mujeres con dilatación cervical prematura/cuello corto, encontrando un punto de corte de 2,89 pg/ml, con un área bajo la curva de 0,734 (IC 95%, 0,598–0,870), sensibilidad del 66,7% y especificidad del 70,1%, mucho más bajos que nuestros resultados en el fluido vaginal.

Segundo artículo:

El cerclaje cervical de emergencia es una opción de tratamiento para prolongar el embarazo y reducir la prematuridad en embarazos únicos y gemelares. La realización de una amniocentesis antes del cerclaje indicado por exploración

física aún es controvertida. Sin embargo, varios autores lo recomiendan debido a que el diagnóstico de corioamnionitis subclínica empeora significativamente el resultado obstétrico. Como ha demostrado este estudio, descartar la inflamación y la infección intraamnióticas en pacientes con insuficiencia cervical en el segundo trimestre del embarazo es esencial para mejorar los resultados perinatales antes de colocar un cerclaje de emergencia.

Recientemente, dos metaanálisis han demostrado que el cerclaje de emergencia está asociado con una mejora significativa en los resultados perinatales tanto en embarazos gemelares como en embarazos únicos con cérvix dilatado. Además, en embarazos gemelares con una longitud cervical <15 mm, el cerclaje cervical está asociado con una reducción significativa del parto prematuro.

La tasa de insuficiencia cervical en gestaciones gemelares es del 5,0%, mientras que en gestaciones únicas es del 0,05–1,8%. En consecuencia, en este estudio, la insuficiencia cervical en embarazos gemelares es más frecuente que en los embarazos únicos, y está asociada con mayores tasas de nuliparidad y el uso de técnicas de reproducción asistida.

La IL-6 es la principal citoquina proinflamatoria liberada en el líquido amniótico en respuesta a la invasión bacteriana. La producción de citoquinas estimula la síntesis de prostaglandinas, las cuales inducen la maduración cervical y su posterior dilatación.

Nosotros realizamos la amniocentesis en las gestaciones únicas y en las gestaciones gemelares únicamente en la bolsa del primer gemelo para descartar inflamación o infección intraamniótica. El cerclaje se colocó solo si la IL-6 era $\leq 2,6$ ng/mL. (alrededor del 65% en ambos tipos de gestación). No se encontraron diferencias en los parámetros del líquido amniótico entre los embarazos gemelares y únicos.

Un total del 27,4% de los cultivos fueron positivos en embarazos únicos con prolapso de membranas en comparación con el 30,76% en embarazos gemelares. La incidencia de cultivos positivos en embarazos únicos y gemelares con insuficiencia cervical es más baja que la reportada por Romero et al. Estos

autores describieron una prevalencia de invasión microbiana de la cavidad amniótica del 51,5% en embarazos únicos. Las diferencias pueden deberse a disparidades socioeconómicas y étnicas entre las poblaciones estudiadas. Mientras que Romero et al, describió que los microorganismos más comunes aislados en pacientes con insuficiencia cervical fueron *Ureaplasma urealyticum*, *Gardnerella vaginalis*, *Candida albicans* y *Fusobacterium* sp. En este trabajo, las bacterias más prevalentes han sido Gram positivas (*Streptococcus* y *Staphylococcus*), seguidas de las Gram negativas (*Fusobacterium* sp., *E. coli*, etc.), *Ureaplasma urealyticum* y *Candida albicans*.

La determinación de IL-6 en el líquido amniótico para descartar inflamación intraamniótica mejora los resultados perinatales de pacientes con embarazos gemelares y únicos.

La principal limitación del estudio es el tamaño de la muestra, especialmente en los embarazos gemelares. No obstante, la concordancia con otros estudios sugiere que los resultados son veraces. La inclusión de datos sobre el cerclaje de emergencia en embarazos gemelares fortalece este trabajo.

Tercer artículo:

En nuestra experiencia, el uso de cerclaje fue beneficioso para reducir los PPE y mejorar los resultados neonatales en mujeres asintomáticas con un embarazo múltiple y cérvix corto detectado por ecografía vaginal en el segundo trimestre. El efecto del cerclaje en nuestra serie fue independiente de otros factores de confusión.

La identificación de un cérvix corto en el segundo trimestre en mujeres asintomáticas con un embarazo múltiple puede representar el subgrupo ideal que podría beneficiarse de un cerclaje. Por lo tanto, consideramos que era de interés realizar una revisión de la literatura, considerando solo aquellos estudios que han analizado el uso de cerclaje en embarazos gemelares asintomáticos con un cuello uterino corto detectado ecográficamente en el segundo trimestre. Hasta donde sabemos, solo existen 3 ensayos controlados aleatorios que incluyen muestras pequeñas de mujeres con embarazos múltiples y un cuello uterino corto que han sido analizados en conjunto en dos revisiones sistemáticas. El resto de la evidencia disponible proviene de estudios de cohortes retrospectivos

y un estudio de casos y controles. Aunque ningún estudio contiene una serie suficientemente grande por sí mismo, los datos combinados en estos estudios suman 273 embarazos gemelares en el grupo de cerclaje y 250 en el grupo de control.

El análisis de los datos de estos estudios sugiere que el cerclaje podría reducir los PPE antes de las 32 semanas en un 48 % en estas mujeres asintomáticas con cuello uterino corto diagnosticado por ecografía transvaginal en el segundo trimestre. Según estos datos, se necesitarían realizar 5 cerclajes para prevenir 1 PPE < 32 semanas. Los resultados neonatales solo se han analizado en un reciente estudio de casos y controles y nuestra propia serie. En ambos estudios, el cerclaje se asoció con una mejora en el resultado neonatal.

Además, un metaanálisis que incluyó 15 estudios con un total de 726 mujeres también concluyó que el cerclaje se asoció con una tasa reducida de partos prematuros en embarazos gemelares con un cuello uterino < 15 mm.

También debe considerarse una preparación adecuada de las mujeres que se someten al cerclaje. En nuestro grupo de cerclaje, la razón para usar indometacina y antibióticos antes de colocar el cerclaje fue tratar el posible síndrome inflamatorio subyacente a la incompetencia cervical. Curiosamente, no se encontraron diferencias entre nuestros grupos de cerclaje y control en la incidencia de RPM o corioamnionitis clínica.

Un estudio previo en mujeres asintomáticas con un embarazo gemelar y un cuello uterino dilatado antes de las 24 semanas también mostró que la combinación de cerclaje, indometacina y antibióticos disminuyó la incidencia de PPE y mejoró el resultado perinatal. En embarazos únicos con cuello uterino corto en el segundo trimestre y sin cerclaje, la indometacina redujo los partos prematuros antes de las 24 semanas, pero no antes de las 35 semanas. Basándonos en estas consideraciones, creemos que el tratamiento con indometacina y antibióticos previo a la colocación del cerclaje es clave para mejorar la tasa de éxito del cerclaje.

Al comparar el cerclaje con otros tratamientos para la prevención del parto prematuro (progesterona vaginal y pesario cervical), debemos considerar no solo la efectividad, sino también los posibles efectos secundarios de cada enfoque terapéutico. El cerclaje es un procedimiento invasivo que requiere anestesia y,

por lo tanto, tiene un mayor riesgo de posibles complicaciones en el momento de la realización.

Cuarto artículo:

En comparación con aquellas con IIA, las pacientes con embarazo gemelar y prolapso de membranas en el segundo trimestre sin IIA que se sometieron a cerclaje de emergencia tuvieron intervalos significativamente mayores desde el diagnóstico hasta el parto y pesos neonatales más altos, así como una incidencia significativamente menor de parto prematuro antes de las 34 semanas y de muerte perinatal. Zeng et al afirmaron que el cerclaje de emergencia en mujeres con insuficiencia cervical se asoció con una disminución general del 40% en el parto prematuro espontáneo antes de las 28 semanas, y la prolongación de la latencia hasta el parto fue de 5 semanas. El predictor más fuerte de parto prematuro espontáneo antes de las 28 semanas después del cerclaje fue un cultivo cervical positivo. Se espera que la primera bolsa amniótica muestre una predominante relación en la inflamación/infección intraamniótica debido a que la ascensión desde el tracto genital inferior es la vía principal para la infección intraamniótica. Curiosamente, Kyung Joon Oh et al. observaron que la presencia de IIA en ambas bolsas amnióticas ocurrió en el 63% (22/35) de los casos.

De los 13 casos restantes, el proceso inflamatorio fue detectable en la primera bolsa amniótica, excepto en un caso. El presente estudio ha obtenido una correlación positiva entre los valores de IL-6 de ambas bolsas amnióticas. Todos los casos con $IL-6 \geq 2,6/mL$ en la primera bolsa amniótica también mostraron $IL-6 \geq 2,6/mL$ en la segunda. Solo dos casos mostraron una $IL-6 \geq 2,6/mL$ en la primera bolsa y una $IL-6 < 2,6/mL$ en la segunda bolsa. Los resultados de ambas gestaciones fueron adversos, igual que cuando la $IL-6$ fue $\geq 2,6/mL$ en ambos sacos. Con estos hallazgos, se puede concluir que podría ser óptimo realizar la amniocentesis solo en la primera bolsa, dado que es la que está más expuesta a un ambiente anormal y el que determinará el pronóstico de la gestación.

La PCR es una proteína reactante de fase aguda inducida principalmente por la acción de IL-6 del gen responsable de la transcripción de PCR durante la fase aguda de un proceso inflamatorio/infeccioso. Existe una correlación entre los niveles crecientes de IL-6 durante las inflamaciones y los niveles crecientes de

PCR. La determinación de esta correlación se utiliza como una herramienta para definir la presencia y el grado del proceso inflamatorio-infeccioso, condicionando actitudes diagnósticas y terapéuticas. La PCR se ha utilizado como un factor pronóstico en infecciones agudas. Shim SS et al. observaron que un umbral de PCR en el fluido vaginal de 10 ng/mL tenía una especificidad del 89% y una sensibilidad del 45% para la identificación de IIA. Las pacientes con concentraciones de PCR en el fluido vaginal superiores a 10 ng/mL tuvieron tasas más altas de parto prematuro en los cinco días, funisitis y corioamnionitis histológica que aquellas con una concentración de PCR en el fluido vaginal por debajo de este umbral. Se estableció un umbral más alto en el suero materno de PCR (17,5 mg/L) para identificar IIA con especificidad similar (96%) y sensibilidad (47%).

Se han observado diferencias significativas en la PCR en sangre materna en el presente estudio. Los valores preoperatorios de PCR < 3,9 mg/dL mostraron una mayor supervivencia. El mismo umbral fue publicado por Minakami et al. Ellos observaron que un valor preoperatorio de PCR $\leq$ 4,0 mg/dL, un recuento de leucocitos $\leq$ 14.000/microL y dilatación cervical $\leq$ 4 cm se asocian significativamente con la prolongación del embarazo después de un cerclaje cervical de emergencia. Además, en 2017 se publicó que los niveles elevados de PCR $\geq$ 0,4 mg/dL (aOR: 0.34; IC 95%: 0.18-0.65) están asociados con una probabilidad significativamente reducida de llegar a las 28 semanas de gestación antes del parto en gestantes con insuficiencia cervical. En el presente estudio, se ha encontrado una correlación entre la PCR y la IL-6. Por lo tanto, la PCR podría ayudar a seleccionar a aquellas pacientes que podrían beneficiarse de la colocación de un cerclaje de emergencia cuando no se pueda realizar una amniocentesis o no se puedan analizar los parámetros del líquido amniótico. No obstante, se necesitan más estudios para evaluar si la PCR en sangre materna podría constituir un parámetro útil para seleccionar a las pacientes que puedan beneficiarse de un cerclaje de emergencia.

Otro hallazgo relevante es la colonización amniótica, es decir, la presencia de un cultivo positivo en ausencia de inflamación (IL-6 <2,6 ng/mL). Se identificaron dos casos con esta característica que cursaron embarazos sin complicaciones, alcanzando las semanas 35 y 36 respectivamente. Esto respalda investigaciones

anteriores que sugieren que la presencia de bacterias en el líquido amniótico, sin un contexto inflamatorio, no implica necesariamente mal pronóstico, y podría deberse a contaminación en el momento de la extracción.

En cuanto a la técnica de cerclaje y el material empleado, se discutió el posible impacto de la sutura trenzada en la microbiota vaginal. Aunque se ha reportado que este tipo de sutura puede inducir disbiosis, se ha optado por mantener su uso (con Mersilene), ya que estudios posteriores no han demostrado diferencias significativas en las tasas de infección materna ni en los resultados neonatales entre distintos materiales. Además, el diseño del estudio no permite comparar entre tipos de cerclaje (McDonald vs. Shirodkar), por lo que futuras investigaciones podrían explorar este aspecto.

Entre las fortalezas del estudio se encuentra la incorporación de datos específicos de gestaciones gemelares, un grupo históricamente excluido de muchos ensayos clínicos. Asimismo, se destaca el análisis de la IL-6 exclusivamente en la primera bolsa amniótica, lo cual simplifica el procedimiento diagnóstico en estos casos. También se considera valiosa la propuesta de utilizar la PCR como marcador alternativo para evitar procedimientos invasivos.

En cuanto a las limitaciones, se reconoce el tamaño muestral reducido, propio de una condición clínica poco frecuente. Además, el protocolo del hospital establece la colocación sistemática del cerclaje en pacientes sin signos de inflamación, por lo que no se pudo incluir un grupo control con manejo expectante. Esto limita la posibilidad de realizar comparaciones directas del impacto del cerclaje frente a no intervenir.

No obstante, esta decisión se justifica con criterios éticos y en el consenso clínico actual, que favorece el cerclaje en ausencia de IIA.

Conclusiones:

Primer artículo: Existe una correlación entre la IL-6 intraamniótica y vaginal en pacientes con insuficiencia cervical durante el segundo trimestre del embarazo. Sin embargo, se necesitan más estudios para evitar la realización de una amniocentesis antes de un cerclaje de emergencia.

Segundo artículo: Los embarazos únicos y gemelares con insuficiencia cervical tienen un comportamiento similar cuando se realiza el cerclaje en ausencia de inflamación/infección intraamniótica.

Tercer artículo: Nuestros datos sugieren que el cerclaje en embarazos gemelares asintomáticos con cuello uterino corto en segundo trimestre puede reducir el parto pretérmino espontáneo y mejorar el resultado neonatal.

Cuarto artículo: En comparación con las pacientes con IIA, aquellas con embarazo gemelar e insuficiencia cervical en el segundo trimestre sin IIA que se sometieron a un cerclaje de emergencia tuvieron un intervalo significativamente mayor desde el diagnóstico hasta el parto, así como una incidencia significativamente menor de parto pretérmino < 34 semanas y muerte perinatal. En el caso de las gestaciones gemelares, podría ser óptimo realizar la amniocentesis solo en la primera bolsa amniótica, dado que es la que está más expuesta a un ambiente anormal y es la que determinará el pronóstico de la gestación, aunque se necesitan más estudios para confirmar esto.

La PCR en sangre materna podría constituir una herramienta útil no invasiva para seleccionar a las pacientes que podrían beneficiarse de un cerclaje de emergencia y así evitar la realización de la amniocentesis.



Diagnosis of intraamniotic inflammation by measuring vaginal interleukin-6 in patients with cervical insufficiency: could amniocentesis be avoided?

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ORIGINAL ARTICLE



Diagnosis of intraamniotic inflammation by measuring vaginal interleukin-6 in patients with cervical insufficiency: could amniocentesis be avoided?

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ABSTRACT

Background: Cervical insufficiency is a recurrent, passive, and painless dilation of the cervix in the second trimester. The etiology is unclear, but there may be an association with subclinical intraamniotic infection. Interleukin-6 (IL-6) production in the amniotic cavity is induced by bacterial invasion, it is the major proinflammatory cytokine released in response to infection. Although the gold standard method to measure it is through an amniocentesis, the procedure constitutes an invasive technique with several associated risks. The objective of this study is to determine if there is a correlation between intraamniotic and vaginal IL-6 in patients with cervical insufficiency and bulging membranes during the second trimester of pregnancy, in order to avoid an amniocentesis before the rescue cerclage.

Methods: A cohort study was performed in which all patients with cervical insufficiency and bulging membranes admitted into our tertiary hospital between 2019 and 2020 were included, and a control group of asymptomatic women in the second trimester of gestation where studied at the same time. Patients with bulging membranes underwent an amniocentesis to quantify amniotic IL-6, and a sample of vaginal fluid for vaginal IL-6 determination was obtained from both the study and the control group.

Results: A total of 20 women were included in each group. Median gestational age at diagnosis was 22 weeks in patients with bulging membranes, and 21 weeks in the control group. Vaginal IL-6 in control group (10.875 pg/mL) is much lower than the study group one (1308.77 pg/mL). In patients with bulging membranes, vaginal IL-6 expression was lower in the vagina than in the amniotic cavity [average IL-6 in the amniotic cavity 26890.07 pg/mL, vs 1308.77 pg/mL in the vagina ($p < .01$)]. Through a Spearman coefficient correlation rank [$\rho = 0.709$ ($p < .001$)], there is a positive correlation between amniotic and vaginal IL-6 values. The best value of this correlation was calculated with the ROC curve, being the area under the curve 0.929 (CI 95% 0.721–0.995), and the cutoff of point less than 61.4 pg/mL (sensitivity 83.33%; specificity 92.86%). Patients with vaginal IL-6 < 61.4 pg/mL associated a longer latency time between diagnosis and delivery, a higher neonatal weight and a lower perinatal mortality. Rescue cerclage in vaginal IL-6 < 61.4 pg/mL was the best predictor of good pregnancy outcome.

Conclusion: There is a correlation between intraamniotic and vaginal IL-6 in patients with cervical insufficiency and bulging membranes during the second trimester of pregnancy. However, further studies are needed in order to considerate the avoidance of an amniocentesis before an emergency cerclage.

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intraamniotic inflammation

Introduction

Classically the definition of cervical insufficiency is a recurrent, passive, and painless dilation of the cervix in the second trimester [1]. Although the etiology is unclear, there may be an association with subclinical infection. In fact, it has been reported that 52% of women admitted between 14 and 24 weeks of gestation

with cervical dilatation of >2 cm, intact membranes, and without active labor have microbial invasion of the amniotic cavity [2].

Interleukin-6 (IL-6) is induced by bacterial invasion, it is the major proinflammatory cytokine released in response to infection. The production of cytokines stimulates the synthesis of prostaglandins, and these induce cervical ripening and its subsequent dilatation [3].

Currently, when a pregnant woman is diagnosed with cervical insufficiency the treatment options are expectant management or placement of an emergent cerclage [4]. Amniocentesis before the rescue cerclage is still controversial, but several authors defend it because the diagnosis of subclinical chorioamnionitis significantly worsens the pregnancy outcome [5,6].

The best way of measuring IL-6 is performing an amniocentesis to obtain amniotic fluid. Intraamniotic IL-6 > 2600 pg/ml predicts a short-latency interval between cerclage and delivery [6,7]. It has been described that IL-6 in the blood of patients with cervical insufficiency is increased compared to those with an uneventful pregnancy, but it has not been demonstrated to have a predictive value of the pregnancy outcome following the emergent cerclage [8].

There is a lack of reports regarding patients with bulging membranes and vaginal IL-6 determination. Vaginal IL-6 has only been studied for the assessment of preterm birth [9].

The aim of this study is to determine if there is a correlation between the amniotic fluid IL-6 and the vaginal IL-6 in patients with cervical insufficiency, to rule out intraamniotic inflammation or infection in order to perform the rescue cerclage.

The secondary objectives are to compare the vaginal IL-6 values in women with uneventful pregnancies and in those with cervical insufficiency during the second trimester, as well as to find the best cutoff vaginal IL-6 level that associates a good pregnancy outcome in patients with cervical insufficiency.

Methods

Study design and participants

A cohort study was performed including all pregnant women with cervical insufficiency and bulging membranes in the second trimester of pregnancy who were admitted to La Fe University Hospital in Valencia, Spain, from January 2019 to October 2020. A total of 20 participants were enrolled in the study group. At the same time, a control group of 20 asymptomatic pregnant women in the second trimester of gestation were also included in the study. The exclusion criteria were: uterine contractions, clinical chorioamnionitis [7], premature rupture of membranes, active bleeding, cervical dilatation >3 cm, fetal congenital anomaly, fetal death, and >18 or <26 weeks gestation [10]. Singleton and twin pregnancies were included.

According to the hospital's protocol [6], at the time of their admission patients with bulging membranes received physical examination as well as vaginal and

abdominal ultrasonography to measure cervical dilatation, to confirm the gestational age and to rule out fetal congenital anomalies. Blood maternal sample and electronic fetal monitoring (EFM) were also performed. All patients underwent an amniocentesis with a 20-gauge 15-cm length needle and a 10-cc aspiration syringe. We extracted 70 cc of amniotic fluid (AF): 10 cc for microbial analysis, 10 cc for biochemical analysis (IL-6, leukocytes, glucose) and additional 50 cc for amnioreduction. Amnioreduction could benefit those patients who subsequently may take advantage of a cervical rescue cerclage. A sample of vaginal fluid was also collected with a cotton swab (through the introduction of the cotton swab in the fornix of the vagina without speculum 30 s) for IL-6 determination.

Intraamniotic inflammation was defined by amniotic IL-6 > 2.5 ng/ml [11].

Subclinical chorioamnionitis was defined by two or more of the following criteria: amniotic glucose < 15 mg/dl, amniotic leukocytes > 50/mm³, positive amniotic leukocyte esterase and amniotic LDH > 410 U/ml [12].

Intraamniotic infection was defined by positive bacterial culture [10].

The control group received ambulatory abdominal and vaginal ultrasonography in the second trimester of pregnancy (21 weeks' gestation), and a sample of vaginal fluid for IL-6 determination.

The study was approved by La Fe University Hospital Ethics Committee. Informed consent was obtained from all participating women.

Assays

The vaginal fluid sample was placed in Amies liquid medium (Copan Diagnostics Inc., Murrieta, CA) and stored at 20 °C until assay. IL-6 concentrations were measured in pg/ml by immunoassay (Immulite 2000, DPC, Los Angeles, CA). The IL-6 kit (L2K6P2) is a two-solid phase immunometric assay, based on the capture of monoclonal antibodies for human IL-6, and posterior polyclonal detection of alkaline phosphate labeled antibodies [13].

Levels of IL-6 of the amniotic fluid were measured with commercially available lateral flow immunoassay designed for the quantitative measurement of human IL-6. Interpretation by Milenia POCScan Reader or PicoScan Systems (MileniaBiotec, Gieben, Germany). The laboratory results were shown within 1 h and a half after extraction. Intra-amniotic inflammation was defined by the presence of amniotic IL-6 levels of 2600 pg/ml [11].

Table 1. Comparison of study and control group characteristics.

	Patients with cervical insufficiency (study group)	Women with uneventful pregnancies (control group)
Age	32	31
Singleton pregnancy	16	18
Twins pregnancy	4	2
Gestational age (weeks)	22	21
Cervical length	0	37.55 mm
Vaginal IL-6	1308.77 pg/ml	10.875 pg/ml

Cervical cerclage placement

All patients with bulging membranes beyond the external cervical os without intraamniotic inflammation, sub-clinical or clinical chorioamnionitis were proposed to receive a rescue cervical cerclage. Those patients who rejected the procedure were treated with bed rest.

McDonald or Shirodkar cerclage techniques were used according to the surgeon's decision at the moment of the procedure. Under spinal anesthesia, prolapsed fetal membranes were replaced with the aid of an inflated Foley catheter (14F, 30-cc balloon; Usin Medical Co., Seoul, Korea), and then cerclage was performed using 5-mm Mersilene tape (Ethicon Inc., Aneau, France).

Statistical analysis

Quantitative data are shown as median (interquartile range) and categorical data as number (proportion). Correlation data was performed using the correlation coefficient of Spearman test. Receiving Operator Characteristic (ROC) curves were calculated for each marker analyzed, obtaining the area under the curve (AUC) and the optimum cutoff point with its sensitivity (Se) and specificity (Sp). We used the Kaplan–Meier curve and Cox regression for the survival analysis and Log-Rank tests for Kaplan–Meier curve comparisons. SPSS 20 (IBM, Chicago, IL) was used for statistical analysis. A p -value $<.05$ was considered significant.

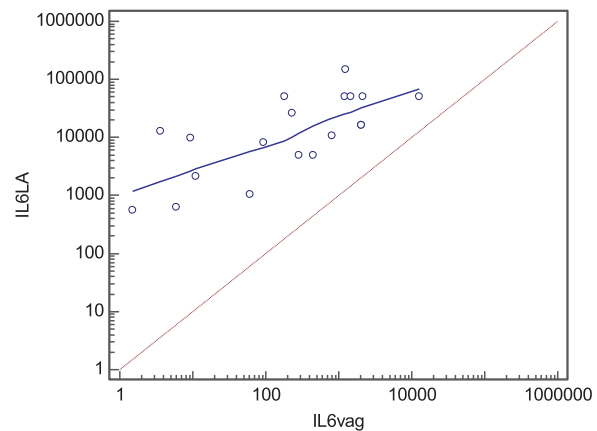
Results

Study population characteristics

In the Table 1 both control and study groups are compared. No significant differences in age and gestational age at the time of the study between pregnant women are found. No differences between single and twin gestations, as well as the gestational age at diagnosis, are seen. The average vaginal IL-6 is higher in patients with bulging membranes when compared with patients with uneventful pregnancies (significant differences).

Sample analysis

In patients with bulging membranes, the vaginal IL6 expression is lower than in the amniotic fluid [average

**Figure 1.** Correlation between amniotic and vaginal IL-6.

intraamniotic IL-6 26890.067 pg/mL, and average vaginal IL-6 1308.77pg/mL ($p < .01$)). Nevertheless, through a Spearman coefficient correlation rank [$\rho = 0.709$ ($p < .001$)] there is a positive correlation between amniotic and vaginal IL-6 values (Figure 1).

The best value of this positive correlation was analyzed in the ROC curve, being the area under the curve 0.929 (CI 95% 0.721–0.995), and the cutoff <61.4 pg/ml (sensitivity 83.33%; specificity 92.86%).

The Table 2 shows the variables of both study groups, which are analyzed based on the indicated cutoff point.

The amniotic fluid IL-6 and glucose levels are clearly different in both groups.

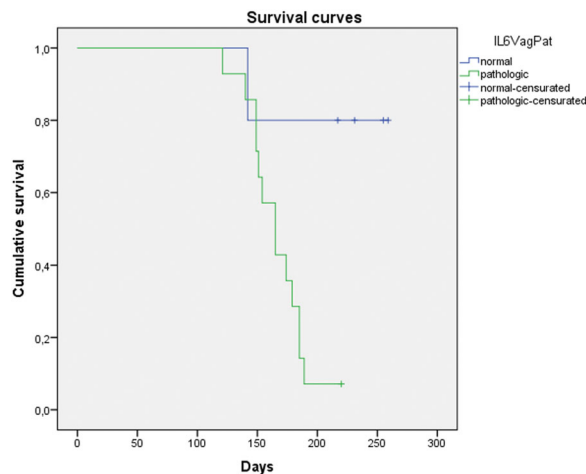
All cases with positive amniotic fluid culture had vaginal IL-6 >61.4 pg/ml. No significant changes in peripheral blood leukocytes were found between the control and the study group, and although the difference in peripheral blood PCR is large, it does not reach statistical significance.

We reject a cerclage in one patient of the first group (vaginal IL-6 <61.4 pg/ml) because amniotic IL-6 was 9662 pg/mL. She suffered a miscarriage 4 d after the amniocentesis. One twin pregnancy has not delivered yet.

There are stark differences between gestational age, latency time between diagnosis and delivery, neonatal weight and perinatal mortality between both groups. Pregnancy outcomes are better in the group with IL-6 <61.4 pg/ml.

Table 2. Variables studied in both groups, divided by ROC curve's cut-off.

	IL6 < 61.4 pg/ml (n = 6)	IL6 > 61.4 pg/ml (n = 14)	p-Value
Maternal age	34 years	31 years	NS
Gestational age (diagnosis)	23 weeks	22 weeks	NS
Singleton pregnancy	5	11	NS
Twin pregnancy	1	3	NS
Cerclage	5	0	$p < .05$
Amniotic IL-6	4456 pg/mL	36,019 pg/mL	$p = .05$
Amniotic glucose	44 mg/dL	25 mg/dL	$p < .05$
Amniotic leucocytes	27/ μ L	498/ μ L	NS
Amniotic LDH	168.83 U/L	470.17 U/L	NS
Amniotic procalcitonin	0.049	0.033	NS
Amniotic + leucocyte esterase	0	5	
Amniotic positive culture	0	4	
Blood leucocytes	14.196	14.154	NS
Blood PCR	4.7	24.95	NS
Gestational age (end)	31 weeks	24 weeks	$p < .01$
Diagnosis/end latency	61 d	12 d	$p < .01$
Late-term abortions	1	7	NS
Vaginal delivery	3	4	NS
Caesareans	1	3	NS
New-born weight	2151 g	851 g	$p < .01$
Mortality	1	10	$p < .05$

**Figure 2.** Survival curves of patients with cervical insufficiency and bulging membranes with vaginal IL-6 above and below 61.4 pg/ml.

In the Figure 2, survival curves of patients with cervical insufficiency and bulging membranes with vaginal IL-6 above and below 61.4 pg/ml can be observed. Patients with IL6 < 61.4 pg/ml associated a higher latency-period between diagnosis of bulging membranes and delivery (Long Rank $p < .001$)

Discussion

It has been reported that the cervicovaginal cytokines remain stable over time in healthy pregnancies [13]. This also observed in our work, given that the IL-6 values in the control group are lower than in the study group. A high vaginal IL-6 concentration corroborates that pregnancy is associated with an active

inflammatory state [14]. Therefore, if vaginal IL-6 is elevated inflammation should be suspected.

The present prospective study highlights that the vaginal IL6 level during the second trimester of pregnancy in patients with cervical insufficiency and bulging membranes is lower than in the amniotic cavity. However, a positive association between intraamniotic and vaginal IL-6 in patients with bulging membranes was found.

The secondary objectives are to compare the vaginal IL-6 values in women with uneventful pregnancies and in those with cervical insufficiency during the second trimester, as well as to find the best cutoff vaginal IL-6 level that associates a good pregnancy outcome in patients with cervical insufficiency.

The amniocentesis is an invasive procedure that entails not only discomfort to the pregnant woman, but it also associates risks for the pregnancy. Nonetheless, its performance prior to the cervical rescue cerclage is essential given that intraamniotic IL-6 constitutes an independent prognostic factor of success or failure of cerclage [6].

The cutoff point of vaginal IL-6 (vaginal IL-6 < 61.4 pg/ml) provides the same prognostic factor for latency period as the amniotic IL-6 level (amniotic IL-6 > 2600 pg/ml), and could prevent the performance of an invasive diagnostic procedure prior to the placement of an emergency cerclage.

To obtain vaginal IL-6 sample is a simple procedure, and it does not require the use of a vaginal speculum, which could tear the amniotic sac and disturb the patient. Moreover, the vaginal IL-6 level is available within 90–120 min.

Vaginal IL-6 expression has never been studied in cervical incompetence. However, it has been analyzed to predict preterm birth. Perales et al., assure that a low cervical IL-6 concentration can accurately identify symptomatic women with a low risk to develop preterm birth, and therefore it avoids unnecessary hospital admissions and side effects of tocolytics and steroids [9].

This preliminary study has provided a cutoff point of vaginal IL-6 (<61.4 pg/ml) in women with cervical insufficiency and bulging membranes that is associated with a low latency period between the diagnosis and the delivery.

In the study, there are two patients with bulging membranes with a low value of vaginal IL-6 and a high value of IL-6 in amniotic fluid. The first one, with vaginal IL-6 9.41 pg/ml and intraamniotic IL-6 9662 pg/ml, had a delivery 4 d after diagnosis of bulging membranes, which suggests a false negative of vaginal IL-6.

The second patient, with vaginal IL-6 3.6 pg/ml and intraamniotic IL-6 12,686 pg/ml, underwent a delivery 69 d after diagnosis of bulging membranes. This suggests a false positive of amniotic IL-6.

While it is true that microbiological information of the amniotic fluid cannot be obtained without an amniocentesis, this study reveals that the amniocentesis and its pregnancy-risks could be avoided before the placement of an emergency cerclage if vaginal IL-6 is determined.

There are studies that evaluate maternal serum levels of IL-6 in patients with cervical insufficiency [8]. Park et al. confirm that increased plasma levels of IL-6 moderately predicted intra-amniotic infection in women with premature cervical dilation/short cervix, they find a cutoff point of 2.89 pg/ml, with an area under the curve of 0.734 (95% CI, 0.598–0.870) sensitivity of 66.7% and specificity of 70.1%, much lower than ours in vaginal fluid [15].

In conclusion, there is a correlation between intra-amniotic IL-6 and vaginal IL-6 in patients with cervical insufficiency and bulging membranes during the second trimester of pregnancy. Further studies are required in order to avoid the performance of an amniocentesis before the placement of the emergency cerclage.

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ORIGINAL ARTICLE



Physical examination-indicated cerclage in twin pregnancies compared with singleton pregnancies

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ABSTRACT

Objective: The aim of this study was to compare pregnancy outcomes of physical examination-indicated cerclage in twin and singleton pregnancies with bulging membranes.

Methods: All women with bulging membranes in the second trimester of pregnancy who were admitted to La Fe University and Polytechnic Hospital from January 2009 to January 2022 were included. A total of 128 participants were enrolled, 102 singleton pregnancies and 26 twin pregnancies. All patients underwent an amniocentesis to rule out intra-amniotic inflammation (IL-6 < 2.6 ng/mL). Cerclage was placed in the absence of intra-amniotic inflammation.

Results: Compared with singleton gestations, twin pregnancies displayed a significantly higher prevalence of nulliparity and assisted reproductive techniques. The incidence of intra-amniotic inflammation/infection was similar in both groups (68.62% in singleton vs. 65.38% in twin pregnancies). The average gestational age of delivery without cerclage in singleton gestations was 23.83 weeks (95% CI 22.82–24.84) and in twin pregnancies, it was 23.69 weeks (95% CI 21.8–25.57). The average gestational age at delivery among patients with cerclage was 37.27 weeks (95% CI 35.35–39.19) in singleton gestations and 36 weeks (95% CI 33.51–38.63) in twin pregnancies, with no significant differences. Time from diagnosis to delivery in patients with IL-6 < 2.6 ng/mL was 79.88 days, and in those with IL > 2.6 ng/mL was 10.87 days. Gestational age at delivery was significantly higher in both singleton and twin pregnancies with cerclage, compared with those without cerclage (log-rank $p < .001$).

Conclusions: Singleton and twin pregnancies with bulging membranes behave similarly when cerclage is placed in the absence of intraamniotic inflammation/infection.

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Cervical insufficiency; physical examination-indicated cerclage; twin pregnancy; singleton pregnancy; amniocentesis; IL-6

Introduction

Preterm birth (PTB) affects 5–18% of pregnancies and is a leading cause of neonatal death [1]. Thus, screening for the risk of PTB is essential in twin [2] and singleton pregnancies [3,4]. A recent study has analyzed the intrauterine and extrauterine variables related to prematurity with statistically significant evidence. Placenta praevia, pregnancy-induced hypertension, antibiotics, cervical length, physical exercise, fetal growth, maternal anxiety, preeclampsia, and antihypertensives increase the risk of prematurity. Thus, an accurate estimation of the risk of PTB can be performed with these factors [5].

Cervical insufficiency is a well-known risk factor for PTB in both singleton and twin pregnancies [6]. It is defined as the inability of the uterine cervix to retain a pregnancy during the second trimester [7]. Twin pregnancies, which have increased dramatically in the latest decades [8] due mainly to assisted-reproductive technology and advanced maternal age at the time of conception, are associated with an increased risk of PTB [9].

Although the etiology of cervical insufficiency is unclear, data suggest an association with subclinical inflammation and infection. Actually, it has been reported that 52% of women admitted between

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14 and 24 weeks of gestation with cervical insufficiency have a microbial invasion of the amniotic cavity [10].

When cervical dilatation and exposed membranes in the second trimester are demonstrated, treatment options include expectant management or placement of a physical examination-indicated cerclage. Physical examination-indicated cerclage is associated with a significant improvement in neonatal survival and prolongation of pregnancy in singleton pregnancies [11–13]. Data are scarce regarding the usefulness of physical examination-indicated cerclage in twin pregnancies with bulging membranes. Thus, the performance of an emergent cerclage in twin pregnancies is not robustly indicated [14]. One study recently published states that prematurity and perinatal mortality are reduced in patients with twin pregnancies and cervical incompetence who undergo cerclage [15]. Moreover, another recent study elegantly shows that physical examination-indicated cerclage in twin pregnancies prolongs latency to delivery similarly to singleton gestations [16]. Thus, the aim of this study was to compare pregnancy outcomes of physical examination-indicated cerclage

between twin and singleton pregnancies with premature cervical dilatation and exposed fetal membranes in the vagina.

Methods

Study design and participants

All pregnant women with bulging membranes in the second trimester of pregnancy who were admitted to La Fe University and Polytechnic Hospital in Valencia, Spain, from January 2009 to January 2022 were included. A total of 128 participants were enrolled in the study, 102 singleton gestations and 26 twin pregnancies (Figure 1 [17]). The McDonald cerclage technique was performed in 16 patients (10 singleton and six twin pregnancies). The Shirodkar type was placed in 23 patients (20 singleton and three twin gestations). Exclusion criteria were uterine contractions, clinical chorioamnionitis [18], premature rupture of membranes, active bleeding, cervical dilatation >3 cm, congenital fetal anomaly, fetal death, and >26 weeks' gestation [19]. Characteristics of singleton and twin pregnancies are shown in Table 1 and Figure 1.

The study was approved by La Fe University Hospital Ethics Committee. Informed consent was obtained from all participating women.

The presence of bulging membranes is defined as the presence of cervical changes of the internal os (e.g. 1 cm dilated or prolapsed membranes) detected on physical examination [20].

According to the hospital's protocol [21], patients with bulging membranes received physical examination as well as vaginal and abdominal ultrasonography at the time of their admission. Blood samples of pregnant patients were obtained, and electronic fetal monitoring was performed. All patients underwent an amniocentesis (in the case of twin pregnancies, only the first amniotic sac was punctured) with a 20-gauge 15-cm length needle and a 10-cm³ aspiration syringe. Within the hospital's protocol, 70 cm³ of amniotic fluid were extracted, 10 cm³ for microbial analysis, 10 cm³

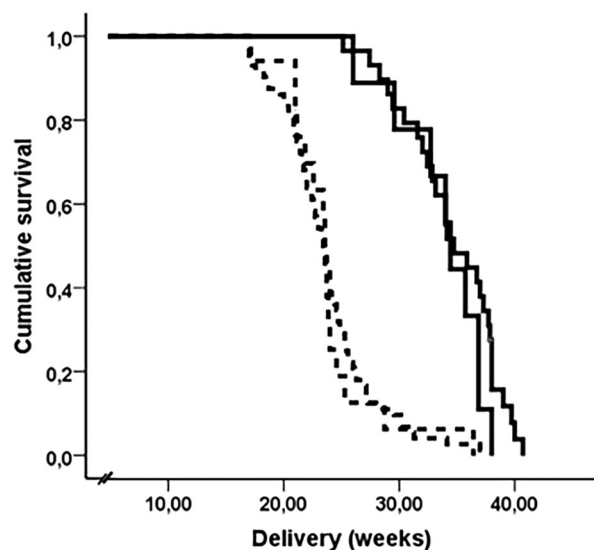


Figure 1. Flowchart of the study design.

Table 1. Basal characteristics and pregnancy outcomes in twin and singleton gestations.

	Singleton pregnancies, <i>n</i> = 102	Twin pregnancies, <i>n</i> = 26	<i>p</i> Value
Average age (years)	33	34	NS
History of preterm labor/late abortion	27 (26.47%)	3 (13%)	NS
Assisted reproductive techniques	12 (13.33%)	13 (50%)	<.001
Nulliparity	72 (70.6%)	24 (92.3%)	<.05
GA at diagnosis (weeks)	22 + 3	21 + 4	NS
Physical examination-indicated cerclage	30 (29.41%)	9 (34.62%)	NS
Time from diagnosis until delivery after cerclage (days)	80	87	NS
Preterm birth < 34 weeks	83 (81.3%)	18 (69.2%)	NS
Perinatal death	48 (47%)	26 (50%)	NS

GA: gestational age; NS: not significant.

for biochemical analysis (IL-6, leukocytes, glucose, leukocyte esterase, LDH, and procalcitonin), and additional 50 cm³ for amnioreduction. Amnioreduction could benefit those patients who subsequently may take advantage of a cervical rescue cerclage [22–24]. Intraamniotic inflammation was defined by amniotic IL-6 >2.6 ng/mL [25]. Intraamniotic infection was determined by positive bacterial culture [19].

Cerclage was placed in the absence of intraamniotic inflammation or infection. Moreover, cerclage was placed if subclinical chorioamnionitis was ruled out. The following criteria defined subclinical chorioamnionitis: amniotic glucose <15 mg/dL, amniotic leukocytes >50/mm³, positive amniotic leukocyte esterase, and amniotic LDH >410 U/mL [26]. Finally, patients with clinical chorioamnionitis did not receive a cerclage. Clinical chorioamnionitis was defined by the following criteria: maternal temperature (>38 °C) and one of these three criteria: fetal tachycardia (>160 bpm during >10 min), serum leukocytosis (>15,000/mm³) or purulent cervical discharge [27].

Assays

Levels of IL-6 in the amniotic fluid were measured with commercially available lateral flow immunoassay designed for the quantitative measurement of human IL-6. Interpretation was carried out by Milenia POCScan Reader or PicoScan Systems (MileniaBiotec, Gieben, Germany). The laboratory results were shown within 90 minutes after the extraction [25].

Cervical cerclage placement

All patients with bulging membranes beyond the external cervical os without intraamniotic inflammation or infection, or subclinical or clinical chorioamnionitis, were proposed to receive a rescue cervical cerclage. Those patients who rejected the invasive procedure or had intraamniotic inflammation/infection or subclinical or clinical chorioamnionitis were treated with bed rest with low-molecular-weight heparin 40 mg subcutaneously (daily) and intravenous antibiotics (ampicillin 1 g every six hours combined with gentamycin 240 mg daily for five days).

McDonald or Shirodkar cerclage techniques were used according to the surgeon's decision at the moment of the procedure. Under spinal anesthesia, prolapsed fetal membranes were replaced with an inflated Foley catheter (14 F, 30-cm³ balloon; Yushin Medical Co., Seoul, South Korea), and then cerclage was performed using 5-mm Mersilene tape (Ethicon

Inc., Auneau, France). Ten trained practitioners carry the procedure out at the tertiary hospital. Before surgery, a 100 mg suppository of indomethacin is administered, and then treatment is maintained for 48 h with 25 mg indomethacin every 8 h. Regarding the type of suture, a study published in 2016 [28] states that braided suture induces a persistent shift toward dysbiosis of the vaginal microbiome characterized by reduction of *Lactobacillus spp.* and enrichment of pathogens causing premature cervical remodeling. We decided to continue using Mersilene suture as a subsequently published study [29] has shown no significant differences in maternal infection rates and adverse neonatal outcomes. There is also no difference in the prolongation of pregnancy when comparing the different suture materials used for the indicated locks.

Statistical analysis

The comparative study used non-parametric tests, the Mann–Whitney *U*-test for quantitative variables and the Kruskal–Wallis test for categorical variables.

The Kaplan–Meier curve was used for the survival analysis, and log-rank tests were applied for the Kaplan–Meier curve comparisons. SPSS 20 (IBM, Chicago, IL) was used for statistical analysis. A *p* value <.05 was considered significant.

Results

Twin pregnancies displayed a significantly higher prevalence of nulliparity and assisted reproductive techniques than singleton gestations. No significant differences were found regarding the mean gestational age at diagnosis of bulging membranes and the interval from diagnosis to delivery. Cerclage was placed in approximately one-third of the patients with singleton and twin pregnancies. No complications during the cerclage or in the postoperative period were observed.

The mean gestation length from diagnosis to delivery in cerclage cases was 11 weeks in singleton pregnancies and 12 weeks in twin pregnancies, with no significant differences in any of the analyzed values.

Two patients with a singleton gestation and IL-6 <2.6 ng/mL did not consent to receive a cerclage. Thus, they received expectant management. One of the patients was diagnosed on day 178 and delivered on day 262. The interval of days from diagnosis to delivery was 84. She spent 69 days at the hospital and had a spontaneous term birth. The newborn's birth

Table 2. Amniotic fluid studied parameters in singleton and twin gestations with bulging membranes in the second trimester of pregnancy.

	Singleton pregnancies, 102	Twin pregnancies, 26	<i>p</i>
Amniotic IL-6	3.64	6.64	NS
IL-6 > 2.6 ng/mL	70 (68.62%)	17 (65.38%)	NS
Glucose	31.3	26.7	NS
Leucocytes	378.14	192.48	NS
DLA	585.63	446.85	NS
Procalcitonin	0.046	0.056	NS
Positive leukocyte esterase	26.58% (21/58)	30% (6/14)	NS
Positive culture	28 (27.45%)	8 (30.76%)	NS

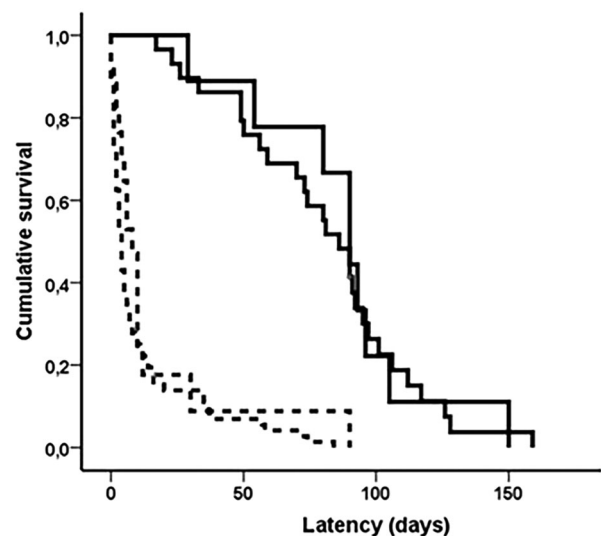
weight was 2840 g. The second patient was diagnosed on day 185 and delivered on day 259. The interval from diagnosis to delivery was 74 days. She was admitted to the hospital for 25 days and had a spontaneous term birth. The newborn's birth weight was 2400 g.

The mean birth weight in singleton pregnancies with cerclage was 2350 g, whereas in those without cerclage was 1012 g. On the other hand, the mean birth weight of the first and second twin in pregnancies with cerclage was 1934 g and 1922 g, respectively, while in pregnancies without cerclage was 675 g and 662 g, respectively, with significant differences ($p < .01$).

No significant differences in the analyzed amniotic fluid parameters were found in singleton and twin gestations (Table 2). The incidence of IL-6 > 2.6 ng/mL was similar in singleton and twin pregnancies, and positive culture was obtained in less than half of the patients.

A total of 28 positive cultures were shown in singleton pregnancies. The most frequent isolated bacteria were Gram + (*Streptococcus* and *Staphylococcus*), which appeared in 14 patients (50%), followed by Gram – (*E. coli*, *Klebsiella*, *Fusobacterium*, etc.), which were detected in seven cases (25%), *Ureaplasma* was isolated in five cases (17.85%), and *Candida albicans* was present in two patients (7.14%). Concerning the eight twin pregnancies with a positive amniotic fluid culture, in four cases Gram + bacteria were detected (50%), in two patients Gram – bacteria were isolated (25%), and in two women *Ureaplasma* was shown (25%).

The gestational age at delivery was significantly higher in both singleton and twin pregnancies with the cerclage, compared with those without the cerclage (log-rank $p < .001$) (Figure 2). Interestingly, the gestational age at delivery was not significantly different in singleton and twin pregnancies with cerclage, and singleton and twin gestations without cerclage (Figure 3 and Table 3 show the perinatal outcomes of patients with bulging membranes according to IL-6 in amniotic fluid).

**Figure 2.** Gestational age at delivery in singleton and twin gestations with (continuous line) and without emergency cerclage (dotted line).

No significant differences were seen regarding the time from diagnosis to delivery in singleton and twin gestations with and without emergency cerclage (Figure 4). The average gestational age at delivery without emergency cerclage was not significantly different in singleton pregnancies (166.8 days [95% CI 159.75–173.88]) compared with twin gestations (165.8 days [95% CI 152.59–179.05]). When emergency cerclage was placed, no differences were also found regarding the gestational age at delivery in singleton gestations (260.9 days [95% CI 247.47–274.37]) compared with twin pregnancies (252.5 days [95% CI 234.62–270.42]).

Discussion

Interpretation

Emergency cervical cerclage has been described as a treatment option to prolong pregnancy and reduce prematurity in singleton and twin pregnancies [11,20,30]. Amniocentesis before the rescue cerclage is

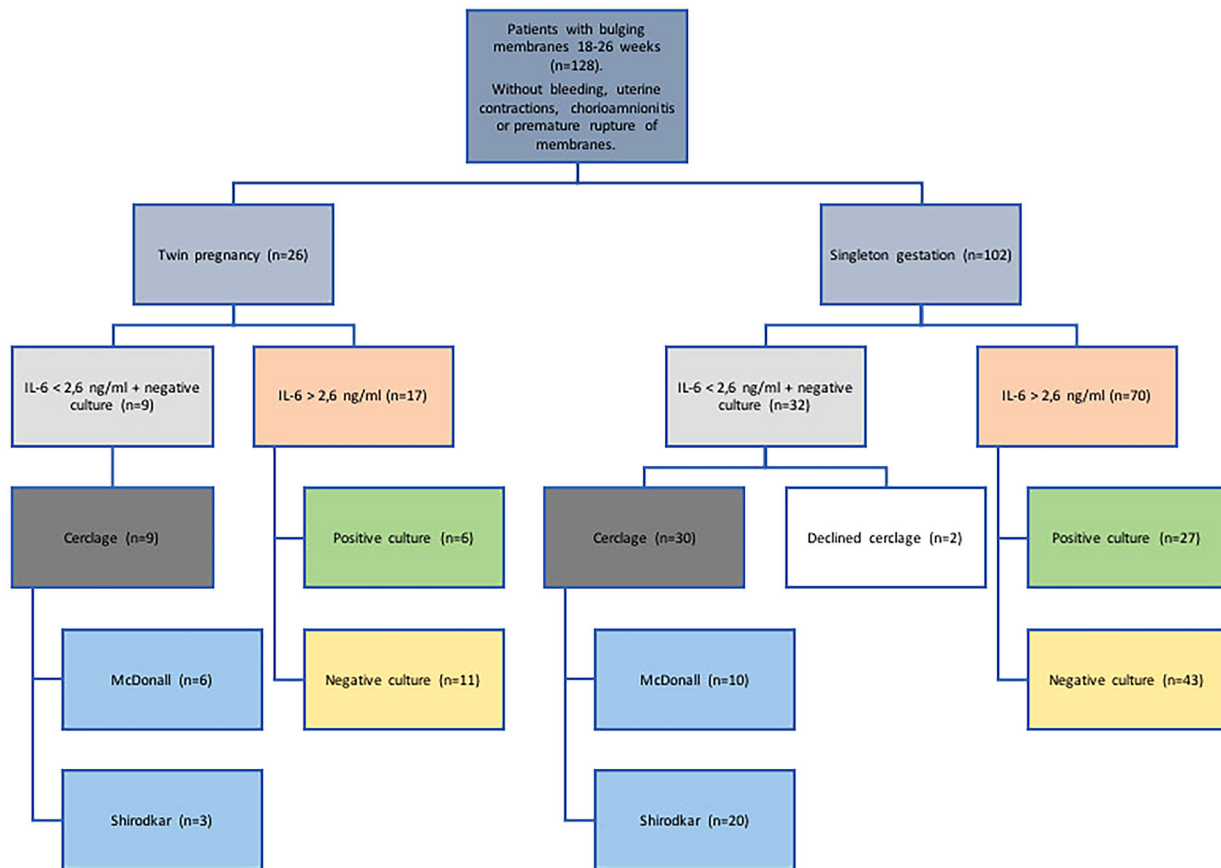


Figure 3. Perinatal outcomes.

Table 3. Pregnancy outcomes in patients without intra-amniotic inflammation or infection and patients with it and patients with intra-amniotic infection.

	IL-6 < 2.6 ng/mL (n = 41)	IL-6 > 2.6 ng/mL and positive culture (n = 33)	p
Gestational age at delivery (weeks ± standard deviation)	34.32 (±4.24)	23.54 (±3.84)	p < .01
Interval from diagnosis to delivery (days ± standard deviation)	79.88 (±34.87)	10.87 (±17.26)	p < .01
Birth < 34 weeks (n)	19	82	p < .01
Perinatal death (n)	0	58	p < .01
Newborn's weight (median in grams ± standard deviation)	2241.45 (±844.10)	962.30 (±40.83)	p < .01

still controversial. However, several authors suggest it because the diagnosis of subclinical chorioamnionitis significantly worsens the pregnancy outcome [21,31]. As this study has shown, ruling out intraamniotic inflammation and infection in patients with bulging membranes in the second trimester of pregnancy is essential to improve perinatal outcomes before placing an emergency cerclage.

Recently, two meta-analyses have demonstrated that emergency cerclage is associated with a significant improvement in perinatal outcomes in both twin and singleton pregnancies with a dilated cervix [12]. In addition, for twin pregnancies with a cervical length <15 mm, cervical cerclage is associated with a significant reduction of PTB [32].

In twin pregnancies, the rate of cervical insufficiency is 5.0%, which is significantly greater than in

singleton pregnancies (0.05–1.8%) [3]. Accordingly, in this study, cervical insufficiency in twin gestations appears earlier than in singleton gestations, and it is associated with higher rates of nulliparity and assisted reproductive technologies.

Interleukin-6 is the major proinflammatory cytokine released in the amniotic fluid in response to bacterial invasion [33]. The production of cytokines stimulates the synthesis of prostaglandins, which induce cervical ripening and its subsequent dilatation [5].

Main findings

In this study, amniocentesis of the presenting twin and in the singleton pregnancy to rule out intra-amniotic inflammation or infection was performed. Cerclage was placed only if IL-6 was ≤2.6 ng/mL

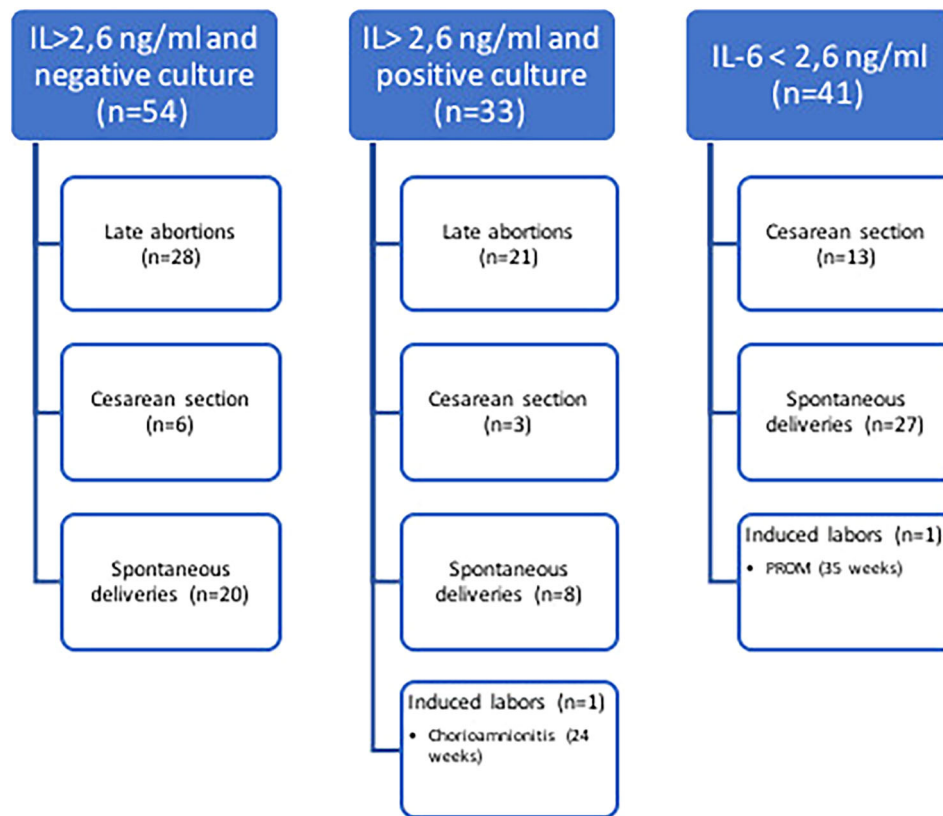


Figure 4. Time from diagnosis to delivery in singleton and twin pregnancies according to the placement of an emergency cerclage. Dotted line without cerclage and continuous line with cerclage.

(around 65% in both types of gestation). No differences were found in the amniotic fluid parameters between twin and singleton gestations.

A total of 27.4% of cultures were positive in singleton gestations with bulging membranes, compared to 30.76% in twin gestations. The incidence of positive culture among singleton and twin pregnancies with bulging membranes is lower than that reported by Romero et al. [10]. These authors described a prevalence of microbial invasion of the amniotic cavity of 51.5% in singleton pregnancies. The differences may be due to socioeconomic and ethnic dissimilarities between study populations. Whereas Romero et al. [10] described that the most common microorganisms isolated in patients with cervical insufficiency were *Ureaplasma urealyticum*, *Gardnerella vaginalis*, *Candida albicans*, and *Fusobacterium sp.* [10], in this work, the most prevalent bacteria have been Gram-positive (*Streptococcus* and *Staphylococcus*), followed by Gram-negative (*Fusobacterium sp.*, *E. coli*, etc.), *Ureaplasma urealyticum*, and *Candida albicans*.

The determination of IL-6 in the amniotic fluid to rule out intraamniotic inflammation improves the perinatal outcomes of patients with twin and singleton

pregnancies who require a cerclage indicated by physical examination. It would be very interesting to avoid amniocentesis before the cerclage to reduce the possible complications of the invasive technique. A prior study of our group demonstrated that vaginal IL-6 correlates with intraamniotic IL-6 [34]. Further studies could determine whether vaginal IL-6 could be useful in ruling out intraamniotic inflammation.

Strengths and limitations

The study's main limitation is the limited sample size, particularly for twin pregnancies. Nonetheless, the consistency with other studies suggests that the results are reliable. The addition of data regarding emergency cerclage in twin pregnancies strengthens this work.

Conclusions

In the present study, emergency cerclage is associated with advanced gestational age at delivery, higher birth weight, and a prolonged period from diagnosis to delivery in singleton and twin gestations, compared

with those without the cerclage. Given that there is a lack of data regarding pregnancy outcomes of emergency cerclage in twin pregnancies, the present findings could be helpful to counsel patients with a twin gestation and bulging membranes in the second trimester of pregnancy, without intra-amniotic inflammation and infection, who could benefit from a physical examination-indicated cerclage.

Disclosure statement

No potential conflict of interest was reported by the author(s).

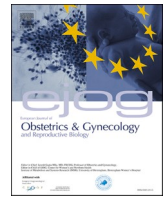
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Full length article

The effectiveness of cervical cerclage in twin pregnancies with a mid-trimester short cervix: A retrospective cohort study

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ABSTRACT

Objective: To analyze the effectiveness of cerclage in twin pregnancies with a short cervix.**Study design:** Retrospective cohort study performed in two University Institutions in Valencia (Spain) with two different protocols for the management of asymptomatic dichorionic diamniotic twin pregnancies with mid-trimester cervical length ≤ 25 mm: treatment with indomethacin, antibiotics and cerclage (cerclage group) (N = 43) versus expectant management (control group) (N = 37).**Results:** The initial cervical length was similar in both groups but detection of a short cervix was performed earlier in the cerclage group (21.6 vs 24.1 weeks, $p < 0.001$). Women with cerclage had a greater pregnancy latency (12.5 vs. 7.7 weeks, $p < 0.001$); higher gestational age at delivery (34.1 vs. 31.8 weeks, $p < 0.04$); less spontaneous preterm birth (SPB) < 28 weeks (11.6 % vs 37.8 %, $p < 0.009$); higher birthweight (2145 vs 1733 g, $p < 0.001$); lower birthweight < 1500 g (12.5 % vs 40.0 %, $p < 0.001$); less admissions to the neonatal intensive care unit (NICU) (24.1 % vs 43.3 %, $p < 0.03$); shorter stay at NICU (25.6 vs 49.4 days, $p < 0.02$); lower respiratory distress requiring mechanical ventilation (14.9 % vs 36.5 %, $p < 0.02$); fewer patent ductus arteriosus (8.9 % vs 26.9 %, $p < 0.008$); and lower composite adverse neonatal outcome (26.6 % vs. 44.8 %, $p < 0.03$). Cerclage and gestational age at diagnosis were the only independent predictors of SPB < 32 and < 28 weeks by multivariate analysis. The cumulative data in the literature show promising beneficial effects of cerclage.**Conclusion:** Our data suggest that cerclage in asymptomatic twin pregnancies with a short cervix may reduce the earliest SPB and may improve neonatal outcome.

Introduction

The worse perinatal outcome of twin pregnancies is mostly influenced by the high rates of preterm births (PB) [1]. The estimated incidence of PB in twin pregnancies is 60 % before 37 weeks, 20 % before 34 weeks and 11 % before 32 weeks [1,2]. Most PB in twin pregnancies are spontaneous PB (SPB) [3].

In asymptomatic women, transvaginal ultrasound measurement of cervical length (CL) before 24 weeks is the best predictor of PB in twin pregnancies, independent of other risk factors [1,2]. The best cut-off at 20–24 weeks for defining a short cervix in twin pregnancies is 25 mm, as

the SPB before 32 weeks increases 3-fold below this limit, whereas a CL above this limit halves this risk [4]. Hence, the predicted probability of SPB in twin pregnancies with a short cervix (≤ 25 mm) at 20–24 weeks is 18.5 % before 28 weeks and 32.2 % between 28 and 32 weeks [1]. Earlier detection of a short cervix increases even more the risk of SPB [1,2].

In singleton pregnancies, a cervical cerclage in women with a previous PB and a CL < 25 mm before 24 weeks was associated with a lower perinatal morbidity and mortality [5]. However, contradictory data can be found regarding the use of cerclage in twins [6,7], probably due to the great difficulty in collecting a sufficiently large sample.

Abbreviations: CL, cervical length; PB, preterm birth; SPB, spontaneous preterm birth.

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The aim of our study was to analyze the effectiveness of cerclage in asymptomatic twin pregnancies with a short cervix and review the data already published. Our working hypothesis was that cerclage might reduce the risk of SPB and adverse neonatal outcome in these high-risk twin pregnancies with an early short cervix.

Materials and methods

Materials

We conducted a retrospective cohort study in asymptomatic women with dichorionic diamniotic twin pregnancies and a short CL (≤ 25 mm) up to 26 weeks of gestation. We compared the different clinical management of these women in two different Institutions attached to the University of Valencia: 43 consecutive women were treated with cerclage at the Instituto Universitario IVI Valencia, and 37 consecutive women with expectant management (control group) at the Hospital Universitario y Politécnico La Fe. The cerclage group included cases collected from 2000 until 2015, while the control group was composed of cases collected from 2012 until 2016. The reason for this discrepancy was that, in the second Institution, CL was not routinely measured in twin pregnancies during the mid-trimester until 2012. No cases were included from 2017 onwards as cerclage in twins with a short CL were also performed in the second Institution. This study was approved by the Instituto Universitario IVI Valencia Ethics Committee on 29th May 2018 (approval no. 1805-VLC-035-VS).

Methods

In the cerclage group, indomethacin (oral 50 mg/8h or rectal 100 mg/12 h), as well as cefuroxime (500 mg/12 h) or vaginal clindamycin (100 mg/day) was administered to all women for 2–3 days prior to the cerclage placement. No amniocentesis were performed at diagnosis. A modified Espinosa-Flores cervical cerclage [8] was performed by the same operator (JF) in all cases, using a mersilene tape. This technique allows anchoring the suture to the cardinal ligaments without dissection of the vaginal mucosa. The suture technique was modified by JF to leave the knots of the mersilene tape at the anterior lip of the cervix. Oral cefuroxime was given postoperatively (500 mg/12 h) until completing 7 days of treatment.

Women in the control group did not receive indomethacin or antibiotics at diagnosis. Instead, an amniocentesis was performed in cases of amniotic sludge and oral azithromycin (1 g/day/5 days) was given only when a subclinical chorioamnionitis was diagnosed with any of the following criteria on the amniotic fluid: positive Gram stain, interleukin 6 > 2.5 ng/ml, leukocytes $> 50/\text{mm}^3$, positive leukocyte esterase ≥ 75 or glucose < 15 mg/dl.

In both groups, tocolytic drugs, followed by vaginal progesterone, were used when uterine contractions were detected. No cervical pessaries were used.

The modified Espinosa-Flores cerclage technique was performed with the urinary bladder empty and the woman in Trendelenburg position. The operator finger was inserted in the cervical canal, as close as possible to the internal cervical os, to be used as a reference guide during the procedure. The needle of the Mersilene tape was inserted at the folding of the posterior lip of the cervix (6 h) with the posterior fornix. The needle was deepened through the middle portion of the cervical stroma in a semi-circular fashion, attempting to reach the lower fibres of both cardinal ligaments at 3 h and 9 h, respectively. Subsequently the needle was turned towards the internal cervical os to avoid the urinary bladder and withdrawing the needle at 12 h at the fold of the anterior lip of the cervix with the anterior vaginal mucosa. In this way, the aim was to have only one entry orifice at 6 h and one exit orifice at 12 h, where 4–5 tight knots were made (after removing the operator's finger from the cervical canal).

The primary outcome measure was the analysis of the perinatal

outcome. The secondary outcome measures included assessment of the risk of SPB < 28 , < 32 , < 34 and < 37 weeks. Finally, we added our series to those already published and analyzed them altogether.

A composite adverse neonatal outcome was defined as the occurrence of any of the following: neonatal death, birthweight < 1500 g, admission to neonatal intensive care unit (NICU), respiratory distress requiring mechanical ventilation, intraventricular hemorrhage grade III–IV, necrotizing enterocolitis grade II–III or sepsis.

Statistical analysis

Statistical analysis was performed using the SPSS program version 20 (IBM SPSS Software, New York, US) and the MedCalc program version 18.10.2 (MedCalc Software, Ostend, Belgium). Categorical and numerical data were described as N (%) and mean (range), respectively. Categorical data were compared using Chi-2 analysis or the Fisher exact test, where appropriate. Numerical data were compared using the unpaired Student *t*-test. A Kaplan-Meier survival analysis with the Mantel-Cox Log Rank test was also conducted to compare the incidence of SPB < 28 and < 32 weeks in both groups. Correlation studies, with the Pearson correlation coefficient, were used to analyze the relationship between numerical variables. A multivariate backwards stepwise binary logistic regression analysis was also performed to rule out influencing factors other than cerclage that could affect the occurrence of SPB. Relative risks with their 95 % confidence interval (CI) and the number of cases needed to treat were also calculated for overall analysis of the literature review. As usual, a *P* value less than 5 % was considered as statistically significant.

Results

Baseline characteristics of both cohorts of women were similar, except for a greater proportion of Caucasian women ($p < 0.02$) and assisted conceptions ($p < 0.001$) in the cerclage group (Table 1). Interestingly, the initial CL was similar in both groups but the diagnosis of a short cervix was performed earlier in the cerclage group ($p < 0.001$) (Table 1).

There was a significant increase in the CL after the cerclage ($p < 0.001$), resulting in a larger CL compared to the control group ($p < 0.001$) (Table 2). The lower the initial CL, the greater the CL increase after the cerclage ($r = -0.370$, $p < 0.02$). CL increase after the cerclage was not correlated with the latency period from diagnosis until delivery ($r = 0.130$, $p = \text{NS}$) or the gestational age at delivery ($r = 0.083$, $p = \text{NS}$). However, there was a positive correlation between the CL 7 days post-cerclage and the gestational age at delivery ($r = 0.333$, $p < 0.04$).

Tocolysis was used more often in the cerclage group ($p < 0.001$)

Table 1

Baseline characteristics of the study population. Results expressed as mean (range) or N (%); (a) Detection of a short cervix (≤ 25 mm); (b) subclinical chorioamnionitis detected in 2 cases; CL: cervical length.

	Cerclage (N = 43)	Control (N = 37)
Age	35.4 (26–48)	33.5 (17–44)
Body mass index (Kg/m ²)	26.7 (20.9–34.5)	27.4 (18.0–37.0)
Caucasian origin	42 (97.7 %)	29 (78.4 %)
Previous early pregnancy losses	16 (37.2 %)	12 (32.4 %)
Nulliparity	40 (93.3 %)	32 (86.5 %)
Previous spontaneous preterm birth	2 (4.7 %)	0 (0 %)
Smoking habit	9 (20.9 %)	4 (10.8 %)
Assisted conception	42 (97.7 %)	23 (62.2 %)
Weeks at diagnosis ^a	21.6 (14.3–26.3)	24.1 (17.3–26.4)
CL at diagnosis ^a (mm)	16.0 (1.7–25.0)	14.9 (0.0–20.0)
CL ≤ 15 mm at diagnosis ^a	20 (46.5 %)	14 (37.8 %)
Amniotic sludge at diagnosis ^a	13 (30.2 %)	5 (13.5 %)
Amniocentesis at diagnosis ^a	0 (0 %)	5 ^b (13.5 %)

Table 2

Obstetric outcome. Results expressed as mean (range) or N (%); CL: cervical length; ROM: rupture of membranes; PB: preterm birth (spontaneous + medically indicated); SPB: spontaneous preterm birth; (a) Detection of a short cervix (≤ 25 mm); (b) information missing in 4 cases of the cerclage group & in 1 case of the control group; (c) 2 ROM occurred in the first 48 h after cerclage.

	Cerclage (N = 43)	Control (N = 37)
CL 7 days post-cerclage or diagnosis ^a (mm)	28.1 (14.4–44.0)	14.2 (0.0–30.0)
Change in CL 7 days post-diagnosis ^a (mm)	12.1 (–0.2 – 32.0)	–1.1 (–20.0 – 10.0)
Vaginal progesterone ^b	21 (53.8 %)	14 (38.9 %)
Courses of tocolysis	2.2 (1–6)	0.8 (0–3)
Corticosteroids	30 (69.8 %)	33 (89.2 %)
ROM < 28 weeks	4 ^c (9.5 %)	6 (16.2 %)
ROM < 32 weeks	6 ^c (14.3 %)	6 (16.2 %)
ROM < 34 weeks	10 ^c (23.8 %)	9 (24.3 %)
ROM < 37 weeks	12 ^c (28.6 %)	10 (27.0 %)
Clinical chorioamnionitis	3 (7.3 %)	3 (8.1 %)
Pregnancy induced hypertension	6 (15.0 %)	3 (8.1 %)
Gestational diabetes	4 (10.0 %)	4 (10.8 %)
Weeks at delivery	34.1 (22.1 – 39.1)	31.8 (21.6 – 38.6)
Weeks from diagnosis ^a to delivery	12.5 (1.9 – 21.1)	7.7 (0 – 15.3)
PB < 28 weeks	5 (11.6 %)	14 (37.8 %)
PB < 32 weeks	9 (20.9 %)	15 (40.5 %)
PB < 34 weeks	16 (37.2 %)	19 (51.4 %)
PB < 37 weeks	35 (81.4 %)	28 (75.7 %)
SPB < 28 weeks	5 (11.6 %)	13 (35.1 %)
SPB < 32 weeks	9 (20.9 %)	14 (37.8 %)
SPB < 34 weeks	13 (30.2 %)	17 (45.9 %)
SPB < 37 weeks	18 (41.9 %)	23 (62.2 %)

(Table 2). Women with cerclage had a greater pregnancy latency ($p < 0.001$), higher gestational age at delivery ($p < 0.04$), less PB and SPB < 28 weeks ($p < 0.007$ & $p < 0.02$, respectively) (Table 2). Survival analysis showed that cerclage was associated with less SPB < 28 weeks ($p < 0.01$) and less SPB < 32 weeks at the limit of significance ($p = 0.053$) (Fig. 1).

Cerclage also decreased SPB < 28 weeks in the subgroup of women with a CL ≤ 15 mm compared to the control group (10.0 % vs 42.9 %, $p < 0.05$). The decrease of SPB < 32 weeks in this subgroup of women with a CL ≤ 15 mm did not reach statistical significance (25.0 vs 50.0 %, $p = NS$).

$p = NS$).

In the cerclage group, the interval from diagnosis until delivery was greater when the diagnosis of a short cervix was performed earlier ($r = -0.429$, $p < 0.005$). No such correlation was found in the control group ($r = 0.117$, $p = NS$). In fact, in the control group there was a positive correlation between the gestational age at diagnosis and at delivery ($r = 0.491$, $p < 0.003$).

Neonates from the cerclage group had greater survival rate ($p = 0.05$), higher birthweight ($p < 0.001$), lower birthweight < 1500 g ($p < 0.001$), higher height ($p < 0.001$), less admissions to the neonatal intensive care unit (NICU) ($p < 0.03$); shorter stay at NICU ($p < 0.02$), less need of mechanical ventilation ($p < 0.02$), fewer patent ductus arteriosus ($p < 0.008$) and lower composite adverse neonatal outcome ($p < 0.03$) (Table 3).

A binary logistic regression analysis was performed to rule out that the protective effect of cerclage was not mediated by the potential influence of other variables (origin of the women, assisted conception, gestational age at diagnosis, amniocentesis, progesterone and tocolytics). The results revealed that cerclage and gestational age at diagnosis were the only independent predictors of SPB < 28 weeks ($p < 0.004$ & $p < 0.004$, respectively) and SPB < 32 weeks ($p < 0.04$ & $p < 0.03$, respectively) in our series.

Comment

Findings

In our experience, the use of cerclage was beneficial to reduce early SPBs and improve neonatal outcome in asymptomatic women with a twin pregnancy and short mid-trimester cervix detected by vaginal ultrasound. The effect of cerclage in our series was independent of other confounding factors.

Identification of a mid-trimester short cervix in asymptomatic women with a twin pregnancy may represent the ideal subgroup that could benefit from a cerclage. Thus, we felt it was of interest to perform a literature review considering only those studies that have analyzed the use of cerclage in asymptomatic twin pregnancies with a sonographically detected midtrimester short cervix (Table 4). To the best of our knowledge, there are only 3 RCT that include small samples of women with twin pregnancies and a short CL [9–11], which have been analyzed together in two systematic reviews [12,13]. The rest of the available evidence comes from retrospective cohort studies [6,7,14–19] and one case-control study [20]. Although, no single study contains a sufficiently large series by itself, the combined data for SPB < 32 weeks

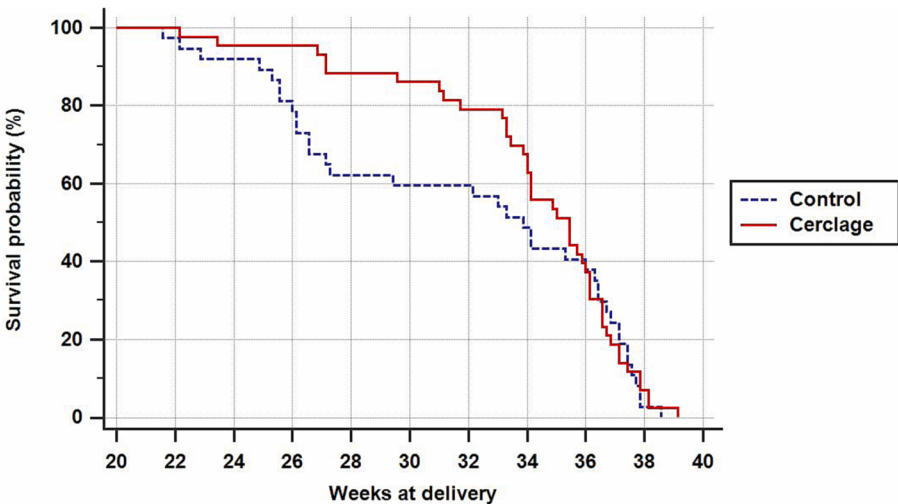


Fig. 1. Survival analysis of on-going pregnancy without delivery in women with cervical cerclage versus expectant management (control group).

Table 3

Perinatal outcome. Results expressed as mean (range) or N (%); NICU: neonatal intensive care unit; (a) all minor anomalies except for 1 case of coarctation of the aorta & auricular septal defect in the cerclage group (delivered at 34 weeks and not requiring admission to NICU or surgical intervention) & 1 case of partial agenesis of the corpus callosum in the control group (both cases had a good outcome).

	Cerclage (N = 86)	Control (N = 74)
Survival	78 (90.7 %)	60 (76.9 %)
Stillbirths	7 (8.2 %)	7 (9.5 %)
Neonatal deaths	0 (0 %)	6 (8.1 %)
Post-neonatal deaths	1 (1.2 %)	1 (1.4 %)
Birthweight	2145.0 (720–3300)	1733.9 (520–3085)
Birthweight < 2500 g	57 (71.3 %)	56 (80.0 %)
Birthweight < 1500 g	10 (12.5 %)	28 (40.0 %)
Height (cm)	44.4 (32–50)	40.9 (30–51)
1 min Apgar	8.5 (1–10)	7.8 (2–10)
1 min Apgar < 7	8/75 (10.7 %)	13/67 (19.4 %)
5 min Apgar	9.5 (3–10)	9.1 (4–10)
5 min Apgar < 7	3/75 (4.0 %)	5/67 (7.5 %)
Admission to NICU	19/79 (24.1 %)	29/67 (43.3 %)
Days in the NICU	25.6 (1–66)	49.4 (1–130)
Congenital anomalies ^a	2/79 (2.5 %)	6/67 (9.0 %)
Respiratory distress requiring mechanical ventilation	16/79 (14.9 %)	27/67 (36.5 %)
Days of ventilation	12.9 (1–60)	25.4 (1–74)
Persistent ductus arteriosus	7/79 (8.9 %)	18/67 (26.9 %)
Pneumonia	1/79 (1.3 %)	2/67 (3.0 %)
Early sepsis	1/79 (1.3 %)	3/67 (4.5 %)
Sepsis	9/79 (11.4 %)	13/67 (19.4 %)
Necrotizing enterocolitis (grade II–III)	1/79 (1.3 %)	5/67 (7.5 %)
Convulsions	0/79 (0 %)	3/67 (4.5 %)
Intraventricular hemorrhage (grade III–IV)	2/79 (2.5 %)	6/67 (9.0 %)
Leukomalacia	1/79 (1.3 %)	3/67 (4.5 %)
Bronchopulmonary dysplasia	3/79 (3.8 %)	7/67 (10.4 %)
Severe retinopathy	2/79 (2.5 %)	0/67 (0 %)
Composite neonatal adverse outcome	21/79 (26.6 %)	30/67 (44.8 %)

in these studies sums up 273 twin pregnancies in the cerclage group and 250 in the control group (Table 4). Analysis of the raw data from such studies suggests that cerclage might reduce SPB < 32 weeks by 48 % in these asymptomatic women with a mid-trimester short cervix diagnosed by transvaginal ultrasound. According to these data, 5 cerclages would need to be performed to prevent 1 SPB < 32 weeks. Neonatal outcomes have only been analyzed in a recent case-control study [20] and our own series. In both of these studies, cerclage was associated with an improved neonatal outcome.

In addition, a meta-analysis that included 15 studies with a total of 726 women also concluded that cerclage was associated with a reduced PB rate in twin pregnancies with a CL < 15 mm [21].

Adequate preparation of women undergoing cerclage also needs to be considered. In our cerclage group, the rationale for using indomethacin and antibiotics before placing the cerclage was to treat the potential inflammatory syndrome underlying cervical incompetence. Interestingly, no differences were found between our cerclage and control groups in the incidence of spontaneous ROM or clinical chorioamnionitis (Table 2). A previous study in asymptomatic women with a twin pregnancy and a dilated cervix before 24 weeks also showed that the combination of cerclage, indomethacin and antibiotics decreased the incidence of SPB and improved perinatal outcome [22]. In singleton pregnancies with a mid-trimester short cervix and no cerclage placement, indomethacin decreased PB < 24 weeks but not PB < 35 weeks [23]. Based on these considerations, we feel that treatment with indomethacin and antibiotics prior to the cerclage placement is of key importance to improve the cerclage success rate.

When comparing cerclage with other strategies for PB prevention (vaginal progesterone and cervical pessary), we need to consider not only the effectiveness but also the potential side effects of each therapeutic approach. Cerclage is an invasive procedure which requires an anesthesia and, thus, has greater risk of potential complications at the time of insertion. With respect to the effectiveness, vaginal progesterone is the only strategy that has shown clear improvements of neonatal outcomes based on data derived from RCT [24,25]. An important RCT on the use of cervical pessaries in this setting also showed a reduction of SPB < 34 weeks but without impacting favorably the neonatal outcomes, except for a reduced incidence of low birthweight (<2500 g) [26].

Strengths and limitations

With respect to previously published series, the principal strength of our work was the analysis of the neonatal follow-up. Another strength was that all cerclages were placed by a single surgeon (JF) at a single institution and using the same technique, which limits confounding factors of cerclage technique or experience. Finally, an unexpected strength of our study was to show the importance of performing an early screening of CL in twin pregnancies, as gestational age at diagnosis of a short cervix was also an independent predictor factor of SPB.

The major limitation of our study was its retrospective approach. In addition, the criticism that the effect of cerclage could also be influenced by other treatments that some women received in both groups has been ruled out by our multivariate analysis. Another important limitation was the low number of cases. Thus, our study, as well as many of the previous studies (Table 4), may be underpowered to detect small differences between the groups. Finally, the different periods of time at which women were treated in both Institutions may also limit the comparison of neonatal adverse outcomes.

Clinical implications

A mid-trimester transvaginal ultrasound CL screening to all twin pregnancies is currently recommended [2]. Women with a twin pregnancy and an early short cervix (<25 mm) have a particularly high risk of SPB [1,2]. Apart from close surveillance, additional measures need to be implemented in this subgroup of women to decrease the risk of SPB. Based on data derived from RCT, we already knew that vaginal progesterone was effective in preventing SPB in this setting [24,25]. Cumulative data derived from small cohort studies (Table 4) also show promising results in favor of a beneficial effect of cerclage for preventing SPB in asymptomatic twin pregnancies with an early short cervix, detected by transvaginal ultrasound.

Research implications

Available evidence on the use of cerclage in twin pregnancies have been mostly obtained from uncontrolled cohort studies (Table 4) and a large collaborative RCT on this issue is still lacking. The additional value of combining vaginal progesterone and cerclage vs using only the former also needs to be properly studied.

Conclusion

Our data suggest that cerclage in asymptomatic twin pregnancies with a short cervix may reduce the earliest SPB and may improve neonatal outcome. The cumulative data in the literature review show promising results in favor of a beneficial effect of cerclage in this setting.

CRedit authorship contribution statement

Jaime Ferro: Investigation, Writing – review & editing. **Vicente Diago:** Conceptualization, Investigation, Validation, Writing – review &

Table 4
Studies on cervical cerclage in twin pregnancies with a sonographically detected mid-trimester short cervix. CL: cervical length; DCDA: dichorionic diamniotic; MCDA: monochorionic diamniotic; SPB: spontaneous preterm birth; PB: preterm birth; w: weeks; N/A: information not available; (a) Weeks at diagnosis or cerclage; (b) expectant management (no-cerclage); (c) subgroup from the total; (d) includes all studies investigating SPB < 32 weeks; (*) statistically significant differences; (#) individual patient data meta-analysis of 3 randomized controlled trials [9–11] (e) [$p < 0.0000$; Relative risk 0.52 (95 % CI 0.40–0.68); relative reduction of risk 0.48 (95 % CI 0.32–0.60); Odds ratio (OR) 0.38 (95 % CI 0.26–0.56); number needed to treat = 4.89 (95 % CI 3.53–7.95)]; (f) [$p < 0.002$; Relative risk 0.53 (95 % CI 0.36–0.78); relative reduction of risk 0.47 (95 % CI 0.22–0.64); Odds ratio (OR) 0.36 (95 % CI 0.19–0.65); number needed to treat = 4.17 (95 % CI 2.66–9.56)].

Author	Type of twins	CL	Weeks ^a	Cerclage	Control ^b	Suture technique	Outcome	Cerclage vs Control
Newman et al. [14]	DCDA & MCDA	≤ 25 mm	18–26	N = 21	N = 12	McDonald	PB ≤ 34 w	9 (42.9 %) vs 6 (50.0 %)
Roman et al. [15]	DCDA & MCDA	≤ 25 mm	14–23	N = 19	N = 12	Modified Shirodkar	SPB < 32 w	4 (21.1 %) vs 3 (25.0 %)
Roman et al. [6]	DCDA & MCDA	≤ 25 mm ≤ 15 mm	16–24	N = 57 N = 32 ^c	N = 83 N = 39 ^c	McDonald (80 %) & Shirodkar (20 %)	SPB < 34 w	29 (50.9 %) vs 53 (63.9 %) 16 (50.0 %) vs 31 (79.5 %)*
Saccone et al. [13] [#]	N/A	≤ 25 mm	< 24	N = 24	N = 25	McDonald	SPB < 32 w	22 (38.6 %) vs 36 (43.4 %)
		≤ 15 mm						13 (40.6 %) vs 22 (56.4 %)
		< 25 mm					PB < 34 w	15 (62.5 %) vs 6 (24.0 %)*
Houlihan et al. [16]	DCDA	< 25 mm	16–24	N = 40	N = 40	Double McDonald	PB < 32 w	11 (45.8 %) vs 4 (16.0 %)*
Adams et al. [17]	DCDA & MCDA	≤ 25 mm	< 24	N = 43	N = 39	McDonald	SPB < 32 w	8 (20 %) vs 20 (50 %)*
	MCDA	≤ 15 mm		N = 27 ^c	N = 21 ^c		PB < 35 w	15 (34.9 %) vs 19 (48.7 %)
Han et al. [7]	DCDA & MCDA	< 25 mm	14–26	N = 36	N = 20	Modified Shirodkar	SPB < 32 w	10 (37.0 %) vs 15 (71.4 %)*
	MCDA	< 15 mm		N = 20 ^c	N = 15 ^c			4 (11.1 %) vs 3 (15.0 %)
Wu et al. [18]	DCDA	< 25 mm	<24	N = 33	N = 13	McDonald	4 (20.0 %) vs 5 (33.3 %) ^c	
		< 25 mm					SPB < 34 w	6 (18.2 %) vs 8 (61.5)*
							SPB < 32 w	3 (9.1 %) vs 6 (46.2 %)*
Yao et al. [19]	DCDA	< 25 mm	16–28	N = 187	N = 133	McDonald	PB < 34 w	115 (61.5%) vs 112 (84.7%)
Qiu et al. [20]	DCDA & MCDA	< 25 mm	18–26	N = 45	N = 45	McDonald	SPB < 34 w	24 (53.3 %) vs 37 (82.2 %)*
	MCDA	<15 mm		N = 24 ^c	N = 24 ^c			13 (54.2 %) vs 20 (83.3 %)*
Present study (2023)	DCDA	< 25 mm	14–26	N = 43	N = 37	Modified Espinosa-Flores	SPB < 32 w	11 (24.4 %) vs 24 (53.3 %)*
		< 15 mm						4 (16.7 %) vs 13 (54.2 %)*
		≤ 25 mm					9 (20.9 %) vs 15 (40.5 %)	
Cumulative data ^d	DCDA & MCDA	≤ 25 mm	14–28	N = 273	N = 250	All the above	SPB < 32 w	61 (22.3 %) vs 107 (42.8 %)
		≤ 15 mm		N = 96 ^c	N = 92 ^c			26 (27.1 %) vs 47 (51.1 %)*,f

editing. **Diana M. Diago:** Writing – review & editing. **Nuria Pellicer:** Investigation. **Inés Olmo:** Investigation. **Sheila Vázquez:** Investigation. **Coral Lara:** Investigation. **Alfredo Perales:** Conceptualization, Formal analysis, Validation. **Vicente Serra:** Conceptualization, Investigation, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Article

Predictive Value of First Amniotic Sac IL-6 and Maternal Blood CRP for Emergency Cerclage Success in Twin Pregnancies

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Abstract: Objectives: To assess the usefulness of first amniotic sac Interleukin-6 (IL-6) to rule out intra-amniotic inflammation (IAI), as well as maternal blood c-reactive protein (CRP), to select patients with a twin pregnancy who may benefit from an emergency cerclage. **Materials and Methods:** Retrospective, descriptive study among all patients with a twin pregnancy and mid-trimester bulging membranes admitted to a tertiary Hospital from January 2012 to September 2023. According to the Hospital's Protocol, all patients received a vaginal and abdominal ultrasound, a maternal blood test, and an amniocentesis of the first sac to rule out IAI, defined by $\text{IL-6} \geq 2.6 \text{ ng/dL}$. **Results:** A total of 28 patients with a twin pregnancy and mid-trimester bulging membranes were included. Among them, 18 patients (64.28%) had IL-6 levels $\geq 2.6 \text{ ng/dL}$. Cerclage was placed in 10 patients with $\text{IL-6} < 2.6 \text{ ng/dL}$. Perinatal mortality in pregnancies with $\text{IL-6} \geq 2.6 \text{ ng/dL}$ was 77.22%. The gestational age at delivery of patients with $\text{IL-6} < 2.6 \text{ ng/dL}$ was 34 ± 3 weeks, compared to 23 ± 4 weeks when IL-6 was $\geq 2.6 \text{ ng/dL}$ ($p < 0.001$). The latency to delivery with $\text{IL-6} < 2.6 \text{ ng/dL}$ was 88.1 ± 31.56 days, compared to 13.11 ± 20.43 days when IL-6 was $\geq 2.6 \text{ ng/dL}$ ($p < 0.001$). Significant differences were found in maternal blood CRP levels in both study groups (no IAI 4.32 ± 3.67 vs. IAI 13.32 ± 15.07 , $p < 0.05$). The area under the curve with an ROC curve was 0.799 (IC 95% 0.596–0.929), with a cut-off of 3.9 mg/L (S 94.4%, % E 62.5%). The gestational age at delivery with $\text{CRP} < 3.9 \text{ mg/L}$ was 33 ± 5 weeks, while in cases with $\text{CRP} \geq 3.9 \text{ mg/L}$, it was 24 ± 5 weeks ($p < 0.001$). The latency days to delivery were 86.5 ± 44.88 and 21.95 ± 30.97 days ($p < 0.01$), respectively. A positive correlation between the IL-6 values of both amniotic sacs was obtained, along with the Spearman coefficient correlation rank ($\rho = 0.835$, $p < 0.001$). **Conclusions:** Compared to those with IAI, patients with a twin pregnancy and mid-trimester bulging membranes without IAI who underwent emergency cerclage had a significantly higher interval from diagnosis to delivery, as well as a significantly lower incidence of preterm birth < 34 weeks and perinatal death. Further studies are needed to assess whether the IL-6 of the first amniotic sac and maternal blood CRP might constitute a useful parameter to select patients who may benefit from an emergency cerclage.



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Keywords: cervical insufficiency; physical examination-indicated cerclage; emergency cerclage; bulging membranes; twin pregnancy; amniocentesis; IL-6; CRP

1. Introduction

Compared to singleton pregnancies, multiple gestations are associated with a higher risk of perinatal morbidity and mortality, particularly due to the elevated incidence of preterm birth (PTB) [1,2]. The incidence of PTB is 59% before 37 and 11% before 32 weeks of gestation [3]. The onset of PTB in twin pregnancies is mainly spontaneous, followed by the preterm premature rupture of membranes. However, a significant proportion of these pregnancies are delivered preterm after iatrogenic-indicated obstetrical interventions [3].

Cervical insufficiency is a well-known risk factor for preterm birth (PTB) in both singleton and twin pregnancies [4–7]. When cervical dilatation and bulging membranes in the second trimester are demonstrated, treatment options include expectant management or the placement of an emergency or a physical examination-indicated cerclage. The available literature has revealed that the emergency cervical cerclage is an effective treatment option for singleton [8,9] and twin pregnancies [10–15] with cervical insufficiency. Nonetheless, the optimal gestational age for cervical cerclage placement and the effectiveness of emergency cervical cerclage in multiple pregnancies remain controversial [16].

Intra-amniotic inflammation/infection constitutes a cause of cervical insufficiency, and its presence is a risk factor for adverse outcomes. The outcome of patients with microbiologically proven intra-amniotic infection is similar to that of patients with intra-amniotic inflammation and a negative amniotic fluid culture. Amniotic fluid interleukin-6 (IL-6) ≥ 2.6 ng/mL without positive amniotic culture indicates intra-amniotic inflammation (IAI) [17,18]. Additionally, maternal blood inflammatory markers such as c-reactive protein (CRP) are associated with PTB [19], and high levels of CRP have been found in patients with the preterm premature rupture of membranes and intra-amniotic inflammation/infection [20].

Thus, this study aimed to assess the usefulness of first amniotic sac IL-6 to rule out IAI, and then maternal blood CRP, to select patients with a twin pregnancy who may benefit from an emergency cerclage.

2. Materials and Methods

2.1. Study Design and Participants

This is a retrospective, descriptive study among all patients with a twin pregnancy and mid-trimester bulging membranes admitted to a tertiary Hospital from January 2012 to September 2023. The study was approved by the Ethics Committee of La Fe University and Polytechnic Hospital (protocol code 2020-271-1 and date of approval 29 April 2020). Informed consent was obtained from all patients. The presence of bulging membranes was defined as asymptomatic cervical dilation of the external os (≥ 1 cm with prolapse of membranes at or beyond the external os) by physical examination in the absence of uterine contractions, or prolapsed membranes detected by physical examination in the absence of uterine contractions [11].

All pregnant women with a twin pregnancy and bulging membranes in the second trimester of pregnancy who were admitted to La Fe University and Polytechnic Hospital, Valencia, Spain, from January 2012 to September 2023, were included. The exclusion criteria were the following: uterine contractions, clinical chorioamnionitis [21,22], premature rupture of membranes, active bleeding, cervical dilatation > 3 cm, fetal congenital anomaly,

fetal death, $<14^{+0}$ weeks gestation, $>26^{+6}$ weeks gestation, and no signature of informed consent by the pregnant woman.

According to the hospital's protocol [23], patients with bulging membranes received physical examination as well as vaginal and abdominal ultrasonography at the time of the hospital admission. Additionally, a blood test to analyze inflammatory markers such as leukocytes and CRP was performed on all pregnant patients. All patients underwent an amniocentesis of the first amniotic sac (only in the 12 first cases were both amniotic sacs punctured) with a 20-gauge 15 cm-long needle and a 10 cc aspiration syringe. Within the hospital's protocol, 70 ccs of amniotic fluid were extracted, 10 ccs for microbial analysis, 10 ccs for biochemical analysis (IL-6, leukocytes, glucose, leukocyte esterase, lactate dehydrogenase (LDH), and procalcitonin), and an additional 50 cc for amnioreduction. Amnioreduction was performed according to the hospital's protocol, despite the absence of a polyhydramnios diagnosis. It was performed given that amnioreduction could benefit those patients who subsequently may take advantage of a cervical rescue cerclage [24–26]. IAI was defined by amniotic IL-6 > 2.6 ng/mL [18]. Intraamniotic infection was determined by the presence of a positive bacterial culture [21].

Cerclage was placed in 10 cases after ruling out IAI. The other 18 cases were treated with bed rest, subcutaneous low-molecular-weight heparin 40 mg/24 h, and intravenous antibiotics (metronidazole 500 mg/8 h, ceftriaxone 1 g/24 h and clarithromycin 500 mg/8 h).

2.2. Assays

Levels of IL-6 in the amniotic fluid were measured with a commercially available lateral flow immunoassay designed for the quantitative measurement of human IL-6. Interpretation by Milenia POCScan Reader or PicoScan Systems (MileniaBiotec, Gieben, Germany). The laboratory results were shown within ninety minutes after the extraction [18]. A blood test to assess inflammatory markers, including leukocyte count and CRP, was performed for all pregnant patients upon hospital admission.

2.3. Cervical Cerclage Placement

The results of the amniotic fluid parameters were usually reported within 2 h, and the cerclage was performed within the first 24 h after the diagnosis. McDonald or Shirodkar cerclage techniques were used according to the surgeon's decision at the moment of the procedure. Under spinal anesthesia, prolapsed fetal membranes were replaced with an inflated Foley catheter (14 F, 30-cc balloon; Yushin Medical Co., Seoul, Republic of Korea), and then cerclage was performed using 5 mm Mersilene tape (Ethicon Inc., Aneau, France). Ten trained practitioners performed the procedure at the tertiary La Fe University and Polytechnic Hospital. Before or immediately after surgery, 2 g intravenous augmentin and 100 mg suppository of indomethacin were administered.

2.4. Statistical Analysis

The comparative study used non-parametric tests, the Mann–Whitney U test for quantitative variables and the Kruskal–Willis test for categorical variables. The kappa concordance index was also used to evaluate the agreement of different parameters.

To determine the clinical utility of the CRP in the prediction of delivery, ROC analysis was used to determine the AUC of CRP that would correctly classify the maximum number of participants. After obtaining a cut-off (Youden's index), the sensitivity, specificity, and positive and negative likelihood ratios (LR) were calculated.

The Kaplan–Meier curve was used for the survival analysis, and Log-Rank tests were applied for Kaplan–Meier curve comparisons. SPSS 25 (IBM, Chicago, IL, USA) was used for statistical analysis. A p -value < 0.05 was considered significant.

3. Results

A total of 28 twin pregnancies were included in the study. All patients showed a cervical dilatation between 1 and 3 cm. The characteristics of the 28 twin pregnancies included in the study are shown in Table 1. The average age of patients was 34 ± 5 years. A total of 26 (92.85%) women were nulliparous. The mean gestational age at diagnosis of bulging membranes was $21 (\pm 2.5)$ weeks. Unfortunately, 18 (64.28%) patients had amniotic IL-6 ≥ 2.6 ng/dL. Cerclage was placed in 10 cases, all with amniotic IL-6 < 2.6 ng/dL, approximately one-third of all included patients. The McDonald cerclage technique was performed in six patients, and the Shirodkar type was placed in four patients. No complications were observed during the cerclage or in the postoperative period. There were six cases with a positive culture and IL-6 > 2.6 ng/dL, as shown in Table 2.

Table 1. Basal characteristics, maternal blood inflammatory markers, and amniotic fluid parameters studied in patients with a twin pregnancy and bulging membranes in the second trimester, according to the presence or absence of intra-amniotic inflammation. Data are shown as mean and standard deviation or percentage.

	IL-6 < 2.6 ng/mL (n = 10)	IL-6 ≥ 2.6 ng/mL (n = 18)	p
Average age (years)	34.6 ± 5.7	33.94 ± 8.55	NS
Nulliparous	9 (90%)	17 (94.44%)	NS
Assisted reproductive techniques	4 (40%)	10 (55.6%)	NS
Previous miscarriage	2 (20%)	4 (22.2%)	NS
Gestational age at diagnosis (weeks)	$21^{2/7} \pm 3$	$21^{6/7} \pm 2$	NS
Blood leukocyte (/mm ³)	$10,684 \pm 2807$	$12,168 \pm 2948$	NS
Blood CRP (mg/dL)	4.32 ± 3.67	13.32 ± 15.07	<0.05
Blood neutrophils (%)	78.5 ± 11.91	77.40 ± 7.34	NS
Blood fibrinogen (mg/dL)	627.4 ± 71.17	624.29 ± 78.74	NS
Amnionic glucose (mg/dL)	30.90 ± 19.63	22.61 ± 9.71	NS
Amnionic leukocyte (/μL)	69.4 ± 95.15	246 ± 693.32	NS
Amniotic LDH (U/L)	200 ± 85.88	576.6 ± 698.39	$=0.058$
Amniotic procalcitonin (ng/mL)	0.058 ± 0.032	0.042 ± 0.014	NS
Amniotic positive leukocyte esterase	1/7 (14.2%)	5/14 (35.7%)	NS
Positive culture amniotic fluid	2 (20%)	6 (33.3%)	NS

NS: not significant.

There were two cases with a positive culture and IL-6 < 2.6 ng/dL (bacterial colonization), as shown in Table 3. The isolated bacteria were *Klebsiella oxytoca* and *Staphylococcus coagulase-negative*, respectively. In the first case, we performed a McDonald-type cerclage at 15 weeks and 3 days of pregnancy, and the patient delivered at 36 weeks and 6 days (150 days latency to delivery). The newborns' weights were 2275 g and 2600 g. The other patient was diagnosed with bulging membranes at 22 weeks. She underwent a McDonald-type cerclage and started with uterine contractions at 35 weeks and 5 days of pregnancy. An elective C-section due to the first fetus showing breech presentation was performed (96 days of latency to delivery). The newborns' weights were 2125 g and 2700 g.

Table 2. Patients with IL-6 > 2.6 ng/dL and positive culture. All patients with intraamniotic infection and/or inflammation were treated with intravenous metronidazole 500 mg/8 h, intravenous ceftriaxone 1 g/24 h, and oral clarithromycin 500 mg/8 h for 7 days (if delivery does not occur earlier), whether the culture was positive or not. If the antibiogram showed resistance to any antibiotic, it was changed, although in our case, this was unnecessary.

Case	Bacteria	Treatment	Time of Delivery
Case 1	<i>Streptococcus viridans</i> in both amniotic sacs	Metronidazole 500 mg/8 h, ceftriaxone 1 g/24 h and clarithromycin 500 mg/8 h 6 days.	Delivery 6 days after diagnosis.
Case 2	<i>Ureaplasma</i> spp. in both amniotic sacs	Metronidazole 500 mg, ceftriaxone 1 g and clarithromycin 500 mg (only 1 dose).	Delivery the same day of diagnosis.
Case 3	<i>Streptococcus sanguis</i> in the first amniotic sac	Metronidazole 500 mg/8 h, ceftriaxone 1 g/24 h and clarithromycin 500 mg/8 h 5 days.	Delivery 5 days after diagnosis.
Case 4	<i>Ureaplasma</i> spp. in the first amniotic sac	Metronidazole 500 mg/8 h, ceftriaxone 1 g/24 h and clarithromycin 500 mg/8 h 12 days.	Delivery 12 days after diagnosis.
Case 5	<i>Streptococcus agalactiae</i> in the first amniotic sac	Metronidazole 500 mg, ceftriaxone 1 g and clarithromycin 500 mg (only 1 dose).	Delivery the same day as diagnosis.
Case 6	<i>Fusobacterium nucleatum</i> in the first amniotic sac	Metronidazole 500 mg/8 h, ceftriaxone 1 g/24 h and clarithromycin 500 mg/8 h 3 days.	Delivery 3 days after diagnosis.

Table 3. Two patients underwent cervical cerclage (IL-6 < 2.6 ng/dL) and had a positive amniotic fluid culture.

Cervical Cerclage (n = 10): Two Cases with Positive Amniotic Fluid Culture	Amniotic Fluid Culture	Gestational Age Cerclage Placement	Gestational Age and Mode of Delivery	Latency to Delivery (Days)	Newborns' Weights
Case 1	<i>Klebsiella oxytoca</i>	McDonald cerclage at 15 ⁺³ weeks	Vaginal delivery at 36 ⁺⁶ weeks	150	2275 g and 2600 g
Case 2	<i>Staphylococcus coagulase-negative</i>	McDonald cerclage at 22 ⁺⁰ weeks	Cesarean section at 35 ⁺⁵ weeks due to regular uterine contractions and first fetus with breech presentation	96	2125 g and 2700 g

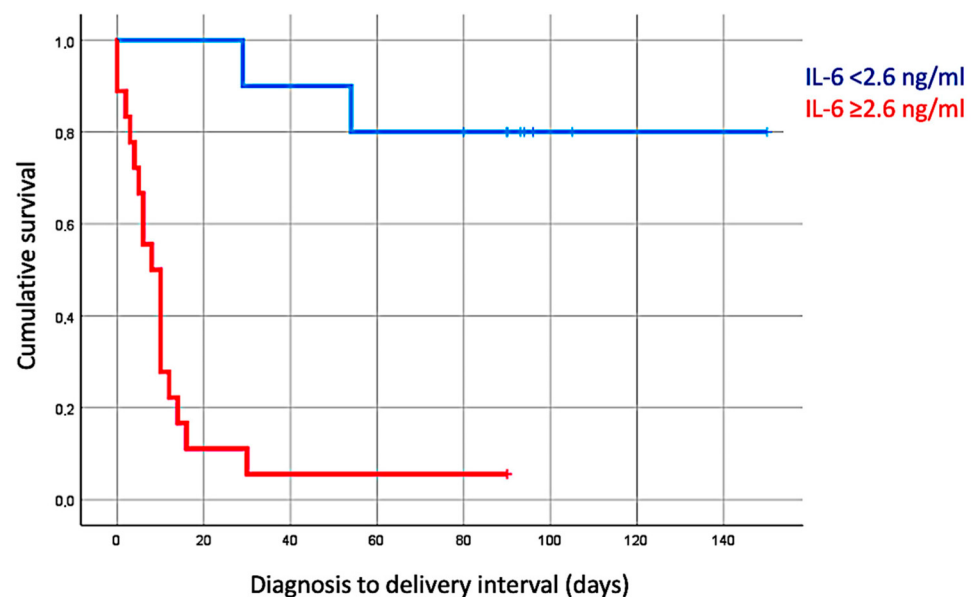
Pregnancy outcomes are shown in Table 4. The perinatal mortality in pregnancies with IL-6 $\geq$ 2.6 ng/dL was 77. 22%. In the group of patients with amniotic IL-6 < 2.6 ng/dL, the survival of the newborns was 100%, and the newborns' weights ranged from 1120 g to 2760 g.

Table 4. Pregnancy outcomes in patients with and without intra-amniotic inflammation.

	IL-6 < 2.6 ng/mL (n = 10)	IL-6 ≥ 2.6 ng/mL (n = 18)	<i>p</i>
Gestational age at delivery (weeks)	34 ^{1/7} ± 3	23 ^{5/7} ± 4	<0.001
Diagnosis-to-delivery interval (days)	88.10 ± 31.56	13.11 ± 20.42	<0.001
Maternal hospital admission (days)	6.60 ± 5.25	8.44 ± 5.32	NS
First newborn birth weight (g)	2008.8 ± 656.26	677.72 ± 505.02	<0.001
Second Newborn birth weight (g)	1992 ± 727.12	664.22 ± 498.92	<0.001
Preterm birth (<34 weeks)	3 (30%)	17 (94.44%)	<0.001
Perinatal death	0	13 (72.22%)	<0.001

NS: not significant.

The average gestational age at delivery with IL-6 < 2.6 ng/dL was 34 ± 3 weeks, compared to 23 ± 4 weeks ($p < 0.001$) in the group with amniotic IL-6 ≥ 2.6 ng/dL. The latency to delivery days with IL-6 < 2.6 ng/dL was 88.1 (±31.56) days, compared to 13.11 ± 20.43 days ($p < 0.001$) in the group with amniotic IL-6 ≥ 2.6 ng/dL. The latency to delivery estimation with IL-6 < 2.6 ng/dL was 18 weeks and 2 days (log-rank 0.001), as shown in Figure 1.

**Figure 1.** Survival of patients with and without intra-amniotic inflammation (log-rank 0.001).

Significant differences were seen in maternal blood CRP when comparing patients with amniotic IL-6 < 2.6 ng/dL and those with IL-6 ≥ 2.6 ng/dL. The area under the curve was calculated based on the ROC curve 0.799 (IC 95% 0.596–0.929), finding a cut-off of 3.9 mg/L (Se 94.4%, Sp 62.5%), a positive LR of 2.52, and a relevant negative LR of 0.089.

The average gestational age at delivery when CRP was <3.9 mg/L was 33 ± 5 weeks, and in cases of CRP ≥ 3.9 mg/L, it was 24 ± 5 weeks ($p < 0.001$), as shown in Table 5. The latency days were 86.5 ± 44.88 days vs. 21.95 ± 30.97 days ($p < 0.01$), respectively. Only one patient had CRP < 3.9 mg/L with IL-6 ≥ 2.6/mL. She delivered at 23 weeks and 3 days, with 10 latency days from diagnosis to delivery. Three patients had CRP ≥ 3.9 mg/L with IL-6 < 2.6 ng/dL. These three patients delivered at 26 weeks, 29 weeks and

4 days, and 37 weeks, respectively, with 29, 90, and 94 latency days from diagnosis to delivery, respectively.

Table 5. Pregnancy outcomes of patients with a twin pregnancy and bulging membranes in the second trimester, according to maternal blood CRP. Two patients lacked data regarding CRP.

	CRP < 3.9 ng/L (n = 8)	CRP ≥ 3.9 ng/L (n = 18)	<i>p</i>
Average gestational age at delivery (weeks)	33 ± 5	24 ± 5	<0.001
Diagnosis-to-delivery interval (days)	87 ± 45	22 ± 31	<0.01
Notes	One patient CRP < 3.9 mg/L and IL-6 ≥ 2.6/mL: delivery 23 ⁺³ weeks (10 days from diagnosis to delivery)	Three patients CRP ≥ 3.9 mg/L and IL-6 < 2.6 ng/dL. Delivery at 26 ⁺⁰ , 29 ⁺⁴ and 37 ⁺⁰ weeks, with 29, 90, and 94 days from diagnosis to delivery, respectively	

Maternal blood CRP was calculated in all patients except two patients due to a laboratory error. In the first case, the IL-6 value in the first amniotic sac was 0.13 ng/dL, and in the second sac it was 0.09 ng/dL; the amniotic fluid culture was negative in both sacs, and the maternal blood leukocytes were 8510/mm³. A McDonald-type cerclage was performed on day 153, and delivery occurred on day 258. The time from diagnosis to delivery was 105 days. The patient underwent a cesarean section, and the neonatal weights were 2760 g and 2680 g. In the second case, the IL-6 of the first amniotic sac was 2.14 ng/dL, the first amniotic sac amniotic fluid culture was negative, and the maternal blood leukocytes numbered 13,010/mm³. A Shirodkar-type cerclage was performed on day 174, and delivery was undertaken on day 238. The time from diagnosis to delivery was 54 days. A preterm premature rupture of membranes was diagnosed at 29 + 2 weeks. The patient underwent a cesarean section, and the neonatal weights were 1820 g and 1760 g.

A positive correlation was obtained between the IL-6 values of both the first and the second amniotic sacs, with Spearman coefficient correlation ranks ($\rho = 0.853$, $p < 0.001$). There were two cases with IL-6 ≥ 2.6 ng/dL in the first amniotic sac and IL-6 < 2.6 ng/dL in the second. The amniotic fluid culture was, in both cases, negative. The agreement between qualitative IL-6 in both sacs was determined. The kappa index was 0.612, $p = 0.001$, which implies a substantial agreement between both parameters.

4. Discussion

Compared to those with IAI, patients with a twin pregnancy and mid-trimester bulging membranes without IAI who underwent emergency cerclage had significantly higher intervals from diagnosis to delivery and newborn weights, and significantly lower incidences of preterm birth < 34 weeks and perinatal death. Additionally, maternal CRP might constitute an additional parameter to help select those patients who may benefit from emergency cerclage.

It has been reported that, in pregnancies with bulging membranes, fetal outcomes significantly improve when cerclage is placed [27]. In addition, in pregnancies with bulging membranes that undergo an emergency cervical cerclage, there are no differences regarding survival between singleton and twin gestations [15]. Thus, emergency cerclage should be considered in both singleton and twin pregnancies.

Zeng et al. [28] stated that emergency cerclage in women with cervical insufficiency was associated with an overall 40% decrease in spontaneous PTB before 28 weeks, and a

prolongation of latency to delivery by 5 weeks. The strongest predictor of spontaneous PTB before 28 weeks after cerclage was a positive cervical culture. The presenting sac is expected to display predominant involvement in intra-amniotic inflammation/infection because the ascension from the lower genital tract is the primary pathway for intra-amniotic infection [17]. Interestingly, Kyung Joon Oh et al. have observed that the presence of IAI in both amniotic sacs occurred in 63% (22/35) of cases. Of the remaining 13 cases, the inflammatory process was detectable in the presenting sac, except for in one case [29]. The present study has obtained a positive correlation between the IL-6 values of both amniotic sacs. All cases with $\text{IL-6} \geq 2.6/\text{mL}$ in the first amniotic sac also displayed $\text{IL-6} \geq 2.6/\text{mL}$ in the second. Only two cases explained in the results section displayed an $\text{IL-6} \geq 2.6/\text{mL}$ in the first sac and an $\text{IL-6} < 2.6/\text{mL}$ in the second sac. The outcomes of both gestations were adverse, the same as when IL-6 was $\geq 2.6/\text{mL}$ in both sacs. With these findings, it can be concluded that it might be optimal to only perform amniocentesis in the first sac, given that this is the one that is more exposed to an abnormal milieu, and the one that will determine the prognosis of the gestation.

It has been well-documented that emergency cerclage is associated with poor outcomes in the presence of IAI or microbial invasion of the amniotic cavity [30]. In the present study, we aimed to identify twin pregnancies with bulging membranes that might benefit from emergency cervical cerclage by ruling out IAI. For this purpose, IL-6 levels were determined in the first amniotic sac, and patients diagnosed with IAI were managed with antibiotic therapy. Our group has previously demonstrated that IL-6 levels in amniotic fluid may serve as a valuable biomarker for guiding the management of patients with singleton pregnancies and bulging membranes, specifically for the placement of rescue cerclage [23]. Recent studies have suggested that rescue cerclage, combined with macrolide antibiotic therapy, may improve pregnancy and neonatal outcomes in cases of singleton pregnancy and cervical insufficiency complicated by IAI when compared with expectant management. These findings highlight the potential benefit of emergency cerclage placement in singleton pregnancies with bulging membranes even in the context of IAI [31]. Further research is required to evaluate whether combining emergency cervical cerclage with antibiotic treatment in patients with a singleton or a twin pregnancy with bulging membranes and IAI can effectively prolong pregnancy and improve pregnancy outcomes when compared with antibiotic treatment alone.

CRP is an acute-phase reactant protein primarily induced by the IL-6 action of the gene responsible for the transcription of CRP during the acute phase of an inflammatory/infectious process. There is a correlation between increasing levels of IL-6 during inflammations and increasing levels of CRP [32]. The determination of this correlation is used as a tool to define the presence and degree of the inflammatory-infectious process, conditioning diagnostic and therapeutic attitudes [33]. CRP has been used as a prognostic factor in acute infections. Shim SS et al. observed that a vaginal fluid CRP cut-off of 10 ng/mL had a specificity of 89% and a sensitivity of 45% in the identification of IAI [34]. Patients with vaginal fluid CRP concentrations of >10 ng/mL had higher rates of preterm delivery within five days, funisitis, and histologic chorioamnionitis than those with a vaginal fluid CRP concentration below this cut-off 30. A higher cut-off in the maternal serum of CRP (17.5 mg/L) was established to identify IAI with similar specificity (96%) and sensitivity (47%) [20].

Significant differences have been seen in maternal blood CRP in the present study. Preoperative CRP values < 3.9 mg/dL showed a major survival. The same cut-off was published by Minakami et al. They observed that a preoperative CRP value ≤ 4.0 mg/dL, a WBC count $\leq 14,000/\text{microL}$, and cervical dilatation ≤ 4.0 cm were significantly associated with the prolongation of pregnancy after an emergency cervical cerclage [35]. Additionally,

it was stated in 2017 that elevated peripheral C-reactive protein levels ≥ 0.4 mg/dL (aOR: 0.34; 95% CI: 0.180.65) are associated with a significantly reduced likelihood of reaching 28 weeks' gestation before delivery in pregnant women with bulging membranes [36]. A recent study stated that the stronger predictors of spontaneous PTB before 28 weeks after an emergent cervical cerclage were pre-operation WBC $> 11.55 \times 10^9$ /L, CRP > 10.1 mg/dL, and cervical dilation > 3.5 cm [37]. Other studies support this [38]. In the present study, a substantial agreement between CRP and IL-6 has been found. Thus, CRP could help to select those patients who may benefit the most from an emergency cerclage placement when amniocentesis cannot be performed, or the analysis of amniotic fluid parameters cannot be carried out. Nonetheless, further studies are needed to assess whether maternal blood CRP might constitute a useful parameter to select patients who may benefit from an emergency cerclage.

Another important finding of this study is the observation of amniotic colonization, defined as a positive amniotic culture with IL-6 < 2.6 ng/dL [39]. It has been described that those pregnant patients with amniotic colonization had similar outcomes to those with negative fluid, defined by IL-6 < 2.6 ng/dL [39,40]. This finding has also been observed in the present study. There were two cases with a positive culture and IL-6 < 2.6 ng/dL, indicative of bacterial colonization. Both cases underwent an emergency cervical cerclage, and delivered at 36 weeks and 6 days (with a latency of 150 days) and at 35 weeks and 5 days (96 days of latency to delivery), respectively. Thus, a positive amniotic fluid culture with IL-6 < 2.6 ng/mL, also known as early colonization [39,40], did not adversely impact the progression or prognosis of these two pregnancies. Previous reports have indicated that the isolation of microorganisms from amniotic fluid in the absence of IAI is indicative of a benign condition [39,40] most likely reflecting contamination during the specimen collection or laboratory processing, rather than early colonization or infection [40].

Regarding the type of suture used for the emergency cerclage, a study published in 2016 [41] states that a braided suture induces a persistent shift towards dysbiosis of the vaginal microbiome, characterized by a reduction in *Lactobacillus* spp. and the enrichment of pathogens causing premature cervical remodeling. We decided to continue using a Mersilene suture for both types of emergency cerclage, McDonald and Shirodkar, as a subsequently published study [42] has shown no significant differences in maternal infection rates and adverse neonatal outcomes. There is also no difference in the prolongation of pregnancy when comparing the different suture materials used for the indicated locks.

The present study was not designed to compare the outcomes of different types of emergency cerclage (McDonald vs. Shirodkar). Furthermore, the limited sample size precluded any such comparative analysis. Future research may focus on evaluating pregnancy outcomes according to the specific type of emergency cerclage performed.

Concerning previously published series, the principal strength of our work is that it improves the current knowledge on treating cervical insufficiency in twin gestations. Importantly, this study is one of the few available studies providing data supporting the assessment of intra-amniotic IL-6 exclusively from the first amniotic sac in twin pregnancies with bulging membranes. Additionally, it is one of the few studies to explore the potential usefulness of maternal blood CRP as a non-invasive alternative to amniocentesis, which is an invasive procedure. The primary limitation of this study is the limited sample size, attributable to the low incidence of the pathology. Additionally, according to the Hospitals' Protocol, all patients without intra-amniotic inflammation or infection underwent emergency cervical cerclage. This protocol inherently precluded the inclusion of a comparison group of patients without intra-amniotic inflammation or infection who did not receive a cerclage, which could have allowed for a direct analysis of the impact of emergency cerclage in these cases. Nonetheless, comparing the outcomes of cerclage placement versus no

cerclage in patients with twin pregnancies and bulging membranes without intra-amniotic inflammation or infection raises ethical challenges, given the current clinical consensus strongly favoring cerclage in such scenarios.

5. Conclusions

In the present study, compared to those with IAI, patients with a twin pregnancy and mid-trimester bulging membranes without IAI who underwent emergency cerclage had a significantly longer diagnosis-to-delivery interval, higher mean gestational age at delivery, higher mean birth weight, and a significantly lower incidence of preterm birth < 34 weeks and perinatal death. Further studies are needed to assess whether maternal blood CRP might constitute a useful non-invasive tool to select patients who may benefit from an emergency cerclage.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The authors can provide additional information regarding the database upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

Intra-amniotic inflammation (IAI), c-reactive protein (CRP), preterm birth (PTB), interleukin-6 (IL-6).

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DISCUSIÓN

El parto pretérmino (PP) afecta al 5-18% de los embarazos y es una de las principales causas de morbilidad y mortalidad neonatal¹. Por lo tanto, la detección del riesgo de PP es esencial en embarazos múltiples² y en embarazos únicos^{3,4}. Un estudio reciente ha analizado las variables intrauterinas y extrauterinas relacionadas con la prematuridad, proporcionando evidencia estadísticamente significativa. Las variables que modifican el riesgo de PP son: la placenta previa, la hipertensión inducida por el embarazo, los antibióticos, la longitud cervical, el ejercicio físico, el crecimiento fetal, la ansiedad materna, la preeclampsia y los antihipertensivos. Por lo tanto, una estimación precisa del riesgo de PP se puede realizar con estos factores⁵.

Los embarazos múltiples, que han aumentado drásticamente en las últimas décadas⁶, debido principalmente a la tecnología de la reproducción asistida y a la edad materna avanzada en el momento de la concepción. Están asociados con un mayor riesgo de morbilidad y mortalidad perinatal, particularmente debido a la elevada incidencia de PP^{7,8}. La incidencia de PP en gestaciones múltiples es del 59% antes de las 37 semanas y del 11% antes de las 32 semanas de gestación⁷. La causa de PP en embarazos múltiples es principalmente espontánea, seguido de la rotura prematura de membranas. Sin embargo, una proporción significativa de estos embarazos pretérmino son inducidos de manera iatrogénica por intervenciones obstétricas necesarias⁷.

En mujeres asintomáticas, la medición transvaginal de la longitud cervical (LC) entre las 18-24 semanas de gestación, es el mejor predictor de PP en embarazos únicos y múltiples, independientemente de otros factores de riesgo^{9,10}. El punto de corte para definir un cérvix corto en estas semanas es de 25 mm¹¹. El riesgo de PP en gestaciones gemelares antes de las 32 semanas se incrementa 3 veces por debajo de este límite, mientras que una LC por encima de este límite reduce a la mitad el riesgo de PP¹². Por lo tanto, la probabilidad de PP en embarazos múltiples con cuello corto (≤ 25 mm) entre las 20 y 24 semanas es del 18.5 % antes de las 28 semanas y del 32.2 % entre las 28 y 32 semanas⁹. Cuanto más temprana sea la detección del cérvix corto, mayor riesgo de PP^{9,10}.

En gestaciones únicas asintomáticas con cérvix ≤ 25 mm con o sin factores de riesgo, se ha reportado que la administración de 200 mg al día de progesterona vaginal micronizada reduce el parto pretérmino < 34 semanas¹³ y las complicaciones neonatales¹⁴. En el caso de las gestaciones gemelares, dada la controversia que existe en diferentes estudios^{15,16}, no hay suficiente evidencia para recomendar su uso.

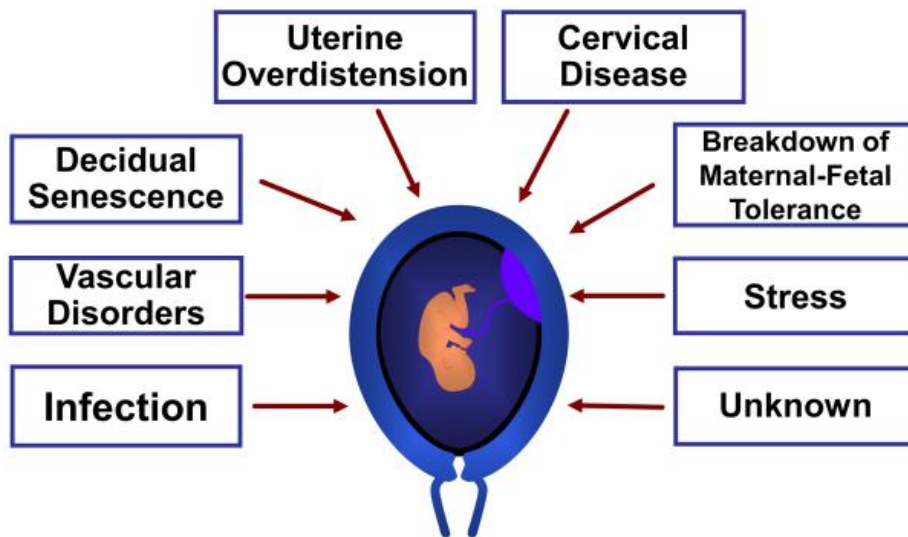
En embarazos únicos, la realización de un cerclaje cervical indicado por ecografía en mujeres con antecedente de PP previo y una LC < 25 mm antes de las 24 semanas se asoció con una menor morbilidad y mortalidad perinatal¹⁷. Sin embargo, en el caso de gestaciones gemelares hay publicados estudios contradictorios^{18,19}, probablemente debido a la gran dificultad de recopilar una muestra suficientemente grande.

En nuestra experiencia, el uso de cerclaje fue beneficioso para reducir los PPE y mejorar los resultados neonatales en mujeres asintomáticas con un embarazo múltiple y cérvix corto detectado por ecografía vaginal en el segundo trimestre. El efecto del cerclaje en nuestra serie fue independiente de otros factores de confusión. Los datos acumulados en la revisión de la literatura muestran resultados prometedores a favor de un efecto beneficioso del cerclaje en este contexto.

Por otro lado, la insuficiencia cervical (IC), es un factor de riesgo para el PP tanto en embarazos únicos como en embarazos múltiples²⁰. La definición clásica de insuficiencia cervical es: dilatación recurrente, pasiva e indolora del cuello uterino en el segundo trimestre²¹. La incapacidad del cuello uterino para retener un embarazo durante el segundo trimestre²². La etiología de la IC puede ser multifactorial y en muchos casos no se identifica una causa única. Algunos factores de riesgo conocidos son: malformaciones uterinas, traumatismos cervicales (conización, legrado...), factores genéticos, hormonales o infecciones²³. La tasa de insuficiencia cervical en gestaciones gemelares es del 5,0%, mientras que en gestaciones únicas es del 0,05–1,8%³. Se ha reportado que el 52% de las mujeres ingresadas entre las 14 y 24 semanas de gestación

con dilatación cervical >2 cm, membranas intactas y sin trabajo de parto activo presentan invasión microbiana de la cavidad amniótica ²⁴.

Figura 1. Factores etiológicos que intervienen en la IC²⁵.



Actualmente, cuando se diagnostica a una gestante de insuficiencia cervical, las opciones de tratamiento son el manejo expectante o la colocación de un cerclaje de emergencia²⁶.

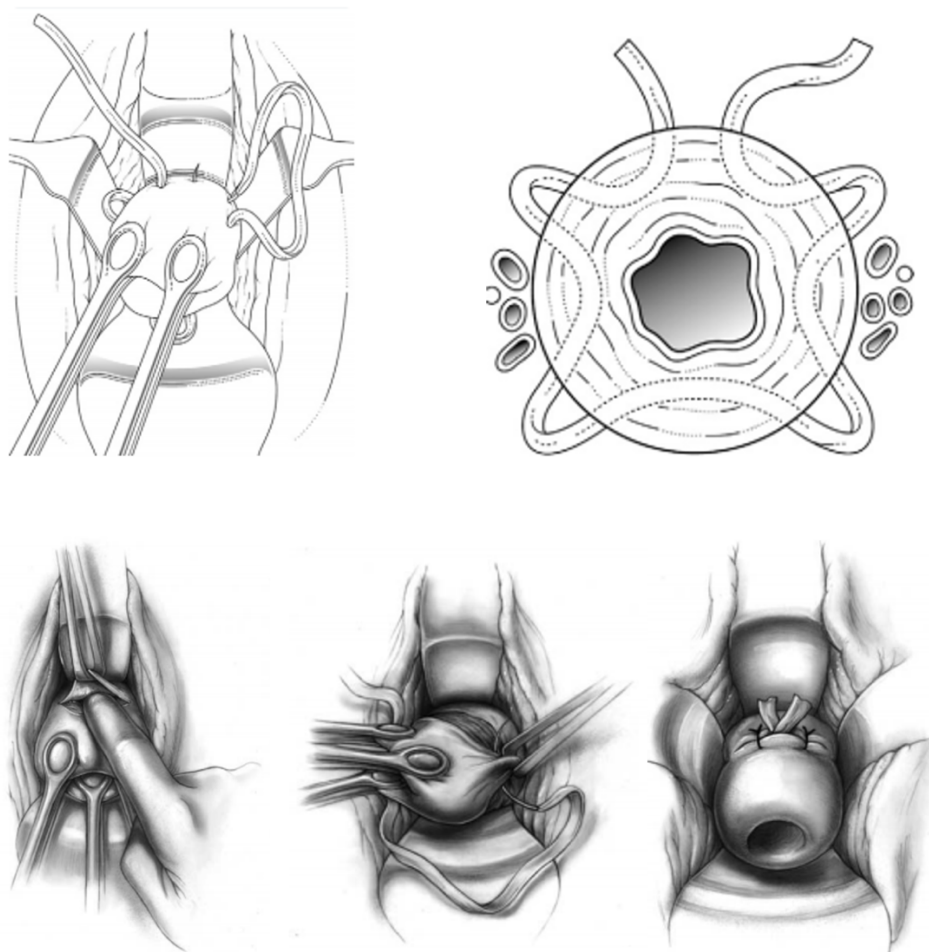
El cerclaje indicado por exploración física está asociado con una mejora significativa en la supervivencia neonatal y la prolongación de la gestación en embarazos únicos ²⁶⁻²⁸ y embarazos múltiples²⁹ con insuficiencia cervical. Sin embargo, la edad gestacional óptima para la colocación del cerclaje cervical y la efectividad del cerclaje cervical de emergencia en embarazos múltiples siguen siendo controvertidas³⁰. Un estudio recientemente publicado afirma que la prematuridad y la mortalidad perinatal se reducen en pacientes con embarazos múltiples e incompetencia cervical que se someten a cerclaje³¹. Además, otro estudio reciente demuestra que el cerclaje indicado por exploración física en embarazos múltiples prolonga la latencia hasta el parto de manera similar a los embarazos únicos²⁹.

Hay numerosas técnicas de cerclaje, pero las más utilizadas son la de McDonald y la de Shirodkar. Aunque en este trabajo también se ha utilizado la técnica de

cerclaje cervical modificada de Espinosa-Flores que está explicada en el tercer artículo de esta tesis doctoral. Las 3 técnicas consisten en realizar un lazo alrededor del cuello por vía transvaginal. Como se puede ver en la figura, el cerclaje Mc Donald consiste en una técnica muy simple, donde sin realizar ninguna incisión, parte de la sutura queda fuera de la mucosa de forma alternante. Es importante profundizar el punto ya que su inserción debe ser en el musculo cervical. En la técnica de Shirodkar, se realiza una colpotomía anterior y otra posterior transversal de 2 cm. En la parte anterior se diseca la vejiga hasta el orificio cervical interno, y en la parte posterior hasta la inserción de los ligamentos útero-sacros. Posteriormente, se pasa la sutura y se anuda, la banda queda enterrada con un anclaje firme y seguro.

El presente estudio no fue diseñado para comparar los resultados de los diferentes tipos de cerclaje de emergencia (McDonald vs. Shirodkar). Además, el tamaño limitado de la muestra impidió realizar dicho análisis comparativo. Investigaciones futuras podrían centrarse en evaluar los resultados obstétricos según el tipo específico de cerclaje de emergencia realizado.

Figura 2. Técnicas de McDonald³² y Shirodkar³³.



En cuanto al tipo de sutura, un estudio publicado en 2016³⁴ indica que la sutura trenzada induce un cambio persistente hacia la disbiosis del microbioma vaginal, caracterizado por una reducción de *Lactobacillus* spp. y un enriquecimiento de patógenos que causan cambios cervicales de forma prematura. Un estudio publicado posteriormente³⁵ ha demostrado que no hay diferencias significativas en las tasas de infección materna ni en los resultados neonatales adversos. Tampoco existe diferencia en la prolongación del embarazo al comparar los diferentes materiales de sutura utilizados para los cerclajes. Por todo esto, en nuestras series se ha utilizado la sutura de Mersilene.

La interleucina-6 (IL-6) es la principal citoquina proinflamatoria liberada en respuesta a la infección provocada por la invasión bacteriana. La producción de citoquinas estimula la síntesis de prostaglandinas, las cuales inducen la maduración cervical y su posterior dilatación ³⁶.

La inflamación/infección intraamniótica constituye una causa de insuficiencia cervical, y su presencia es un factor de riesgo para resultados obstétricos adversos. El resultado obstétrico de las pacientes con infección intraamniótica microbiológicamente comprobada es similar al de las pacientes con inflamación intraamniótica y un cultivo de líquido amniótico negativo. La mejor manera de medir la IL-6 es realizar una amniocentesis. Una IL-6 en el líquido amniótico $\geq 2,6$ ng/mL sin cultivo amniótico positivo indica inflamación intraamniótica (IIA).^{37,38}

La IL-6 intraamniótica $>2,6$ ng/ml predice un intervalo corto de tiempo entre el cerclaje y el parto^{39,40}.

En nuestro trabajo, en comparación con aquellas con IIA, las pacientes con embarazo único o gemelar y prolapso de membranas en el segundo trimestre sin IIA que se sometieron a cerclaje de emergencia tuvieron intervalos significativamente mayores desde el diagnóstico hasta el parto y pesos neonatales más altos, así como una incidencia significativamente menor de parto prematuro antes de las 34 semanas y de muerte perinatal.

En el caso de gestaciones gemelares, tendría sentido analizar únicamente la bolsa amniótica que está en contacto con la vagina, ya que es la que podría estar más expuesta a posibles infecciones. Esto se explica por la teoría de infección ascendente explicada mediante etapas por Romero y Mazor⁴¹. En la primera etapa, hay un sobrecrecimiento de microorganismos patógenos o facultativos en la vagina y cuello uterino. En la segunda etapa, los microorganismos acceden a la cavidad uterina localizándose en la decidua y ocasionando una reacción inflamatoria local y posterior extensión al corion. En la tercera, la invasión alcanza el amnios. En la cuarta y última etapa, las bacterias acceden a la cavidad amniótica del feto por diferentes vías.

El presente estudio ha obtenido una correlación positiva entre los valores de IL-6 de ambas bolsas amnióticas. Todos los casos con IL-6 $\geq 2,6$ /mL en la primera bolsa amniótica también mostraron IL-6 $\geq 2,6$ /mL en la segunda. Solo dos casos explicados en la sección de resultados mostraron una IL-6 $\geq 2,6$ /mL en la primera bolsa y una IL-6 $< 2,6$ /mL en la segunda bolsa. Los resultados de ambas

gestaciones fueron adversos, igual que cuando la IL-6 fue $\geq 2,6$ /mL en ambos sacos. Con estos hallazgos, se puede concluir que podría ser óptimo realizar la amniocentesis solo en la primera bolsa, dado que es la que está más expuesta a un ambiente anormal y el que determinará el pronóstico de la gestación.

Se ha descrito que la IL-6 en la sangre de las pacientes con insuficiencia cervical está aumentada en comparación con aquellas con un embarazo sin complicaciones, pero no se ha demostrado que tenga valor predictivo sobre el resultado obstétrico tras el cerclaje de emergencia⁴².

No existen estudios previos sobre pacientes con insuficiencia cervical y la determinación vaginal de IL-6. La IL-6 vaginal solo se ha estudiado para la evaluación del parto prematuro⁴³ sin insuficiencia cervical.

La realización de una amniocentesis antes del cerclaje indicado por exploración física sigue siendo controvertida, pero varios autores la defienden, ya que el diagnóstico de corioamnionitis subclínica empeora significativamente el resultado obstétrico^{39,44}.

En este trabajo se demuestra, que el punto de corte de IL-6 vaginal (IL-6 vaginal $< 61,4$ pg/ml) proporciona el mismo factor pronóstico que la IL-6 amniótica (IL-6 amniótica > 2600 pg/ml) y podría evitar la realización de un procedimiento diagnóstico invasivo antes de la colocación de un cerclaje indicado por exploración física.

Obtener la muestra de IL-6 vaginal es un procedimiento sencillo y no requiere del uso de un espéculo vaginal, lo que podría rasgar la bolsa amniótica e incomodar a la paciente. Además, el nivel de IL-6 vaginal está disponible en un plazo de 90 a 120 minutos.

A continuación, se comentan dos casos que no se comentaron en el primer artículo porque no se había producido el desenlace del caso en la fecha de aceptación del artículo: se descartó la realización de cerclaje en una paciente del primer grupo (IL-6 vaginal $< 61,4$ pg/mL) porque la IL-6 amniótica era de 9662 pg/mL. Sufrió un aborto espontáneo 4 días después de la amniocentesis. Por otro lado, una paciente de 39 años con 3 abortos previos, gestante mediante FIV ovodonación de un embarazo bicorial biamniótico, ingresó por insuficiencia

cervical con 24 semanas y 6 días. A los 2 días tras descartar IIA (IL-6 amniótica 2135 pg/dL, IL-6 vaginal 10,99 pg/dL y cultivo LA negativo) se realizó un cerclaje de tipo Shirodkar. Con 29 semanas y 4 días fue diagnóstica de RPM que se trata con antibioterapia y reposo hasta la semana 34. Se realiza una cesárea por presentación podálica con peso al nacimiento de la primera recién nacida de 1820 g y de la segunda de 1760 g.

Existen diferencias marcadas entre la edad gestacional, el tiempo de latencia entre el diagnóstico y el parto, el peso neonatal y la mortalidad perinatal entre ambos grupos. Los resultados del embarazo son mejores en el grupo con IL-6 < 61,4 pg/mL.

Estudios recientes han sugerido que el cerclaje indicado por exploración física, combinado con terapia antibiótica con macrólidos, puede mejorar los resultados del embarazo y neonatales en casos de embarazo único e insuficiencia cervical complicada por IIA, en comparación con el manejo expectante. Estos hallazgos destacan el beneficio potencial de la colocación de cerclaje de emergencia en embarazos únicos con prolapso de membranas, incluso en el contexto de IIA⁴⁵. Se requiere más investigación para evaluar si la combinación de cerclaje cervical de emergencia con tratamiento antibiótico en pacientes con embarazo único o gemelar con insuficiencia cervical e IIA puede prolongar efectivamente el embarazo y mejorar los resultados del embarazo en comparación con el tratamiento antibiótico solo.

Además, los marcadores inflamatorios en la sangre materna, como la proteína C-reactiva (PCR), están asociados con PP⁴⁶, y se han encontrado niveles elevados de PCR en pacientes con rotura prematura de membranas y con inflamación/infección intraamniótica ⁴⁷.

Existe una correlación entre los niveles crecientes de IL-6 durante las inflamaciones y los niveles crecientes de PCR⁴⁸. La determinación de esta correlación se utiliza como una herramienta para definir la presencia y el grado del proceso inflamatorio-infeccioso, condicionando actitudes diagnósticas y terapéuticas⁴⁹.

En el presente estudio, se ha encontrado una correlación entre la PCR y la IL-6. Los valores preoperatorios de PCR < 3,9 mg/dL mostraron una mayor

supervivencia. Por lo tanto, la PCR podría ayudar a seleccionar a aquellas pacientes que podrían beneficiarse de la colocación de un cerclaje de emergencia cuando no se pueda realizar una amniocentesis o no se puedan analizar los parámetros del líquido amniótico. No obstante, se necesitan más estudios para evaluar si la PCR en sangre materna podría constituir un parámetro útil para seleccionar a las pacientes que puedan beneficiarse de un cerclaje de emergencia.

Con respecto a las series publicadas previamente, la principal fortaleza de nuestro trabajo fue el análisis del seguimiento neonatal, el hallazgo de la correlación de la IL-6 amniótica con la IL-6 vaginal. Es importante destacar que este estudio es uno de los pocos disponibles que proporciona datos que respaldan la evaluación de la IL-6 intraamniótica exclusivamente del primer saco amniótico en embarazos gemelares con prolapso de membranas. Además, es uno de los pocos estudios que explora la posible utilidad de la PCR en sangre materna como una alternativa a la amniocentesis, que es un procedimiento invasivo. La principal limitación de nuestro estudio fue su enfoque retrospectivo y su bajo número de casos, atribuible a la baja incidencia de la patología. No obstante, la concordancia con otros estudios sugiere que los resultados son veraces. La inclusión de datos sobre el cerclaje de emergencia en embarazos gemelares fortalece este trabajo.

CONCLUSIONES

1. Nuestros datos sugieren que el cerclaje indicado por ecografía en embarazos gemelares asintomáticos con cérvix corto puede reducir los partos prematuros espontáneos más tempranos y mejorar los resultados neonatales. Los datos acumulados en la revisión de la literatura muestran resultados prometedores a favor de un efecto beneficioso del cerclaje en este contexto.
2. El cerclaje indicado por exploración física se asocia con una mayor edad gestacional en el momento del parto, mayor peso al nacer y un período de latencia prolongado desde el diagnóstico hasta el parto en embarazos únicos y gemelares, en comparación con aquellos sin cerclaje.
3. Las pacientes con insuficiencia cervical sin IIA ($IL-6 < 2.6 \text{ ng/mL}$) a las que se les ha realizado un cerclaje indicado por exploración física, tuvieron un intervalo significativamente más largo desde el diagnóstico hasta el parto, una mayor edad gestacional media en el momento del parto, un mayor peso medio al nacer, y una incidencia significativamente menor de parto prematuro < 34 semanas y muerte perinatal.
4. En el caso de las gestaciones gemelares, podría ser óptimo realizar la amniocentesis solo en la primera bolsa amniótica, dado que es la que está más expuesta a un ambiente anormal y es la que determinará el pronóstico de la gestación.
5. El punto de corte de IL-6 vaginal ($IL-6 \text{ vaginal} < 61,4 \text{ pg/ml}$) proporciona el mismo factor pronóstico que la IL-6 amniótica ($IL-6 \text{ amniótica} < 2600 \text{ pg/ml}$) y podría evitar la realización de un procedimiento diagnóstico invasivo antes de la colocación de un cerclaje indicado por exploración física.

6. Se han observado diferencias significativas en la PCR en sangre materna en el presente estudio. Los valores preoperatorios de PCR < 3.9 mg/dL mostraron una mayor supervivencia aunque se necesitan más estudios para evaluar si la PCR en sangre materna podría constituir una herramienta útil no invasiva para seleccionar a las pacientes que podrían beneficiarse de un cerclaje de emergencia.

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ANEXOS

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

D. Antonio J. Orduña Galán, vocal del Comité de Ética de la Investigación con medicamentos del Hospital Universitario y Politécnico la Fe de Valencia, por delegación de la Dra. María Tordera Baviera, titular de la secretaría técnica del Comité de Ética de la Investigación con medicamentos del **Hospital Universitario y Politécnico La Fe,**

C E R T I F I C A

Que este Comité ha evaluado en su sesión de fecha **22 de julio de 2020**, el Proyecto de Investigación:

Título: **“CERCLAJE EN CERVIX INCOMPETENTE DIAGNOSTICADO POR EXPLORACIÓN FÍSICA DURANTE EL SEGUNDO TRIMESTRE.”**

Nº de registro: **2020-271-1**

Versión/fecha de la memoria del proyecto: **29 de abril de 2020**

Versión/fecha de la Hoja de Información al Paciente y Consentimiento Informado: **2/ 09 de junio de 2020**

Que dicho proyecto se ajusta a las normativas éticas sobre investigación biomédica con sujetos humanos y es viable en cuanto al planteamiento científico, objetivos, material y métodos, etc, descritos en la solicitud, así como la Hoja de Información al Paciente y el Consentimiento Informado.

En consecuencia, este Comité acuerda emitir **INFORME FAVORABLE** de dicho Proyecto de Investigación que será realizado en el Hospital Universitario y Politécnico La Fe por la **Dra. Diana María Diago Muñoz** y por el **Dr. Vicente Jose Diago Almela**, ambos del servicio/unidad/grupo de investigación de **OBSTETRICIA Y GINECOLOGÍA**, como Investigadores Principales.

Que el CEIm del Hospital Universitario y Politécnico La Fe, tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm del Hospital Universitario y Politécnico La Fe es la indicada en el anexo I, teniendo en cuenta que, en el caso de que algún miembro participe en el estudio o declare algún conflicto de interés, no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del estudio clínico.

Lo que firmo en Valencia, a 22 de julio de 2020

Firmado por Antonio J. Orduña Galan el
23/07/2020 14:04:36
Cargo: Seguridad y Calidad de los Sistemas
de Información

Fdo.: D. Antonio J. Orduña Galán

ANEXO I

COMPOSICIÓN CEIm

Presidente:

Dra. Adela Cañete Nieto (Oncología Pediátrica)

Vicepresidente:

Dr. Salvador Aliño Pellicer (Catedrático Farmacólogo Clínico)

Secretaria Técnica:

Dra. María Tordera Baviera (Farmacéutica del Hospital)

Miembros:

Dr. Bonaventura Casanova Estruch (Neurología)

Dra. M^a Isabel Izquierdo Macián (Neonatología)

Dr. Luis Vicente Martínez Dolz (Cardiología)

Dra. Paula Ramírez Gallego (Medicina Intensiva - Miembro de la Comisión de Investigación)

Dra. Sara Brugger Frigols (Radiodiagnóstico)

D. Serafín Rodríguez Capellán (Licenciado en derecho - Ajeno a las profesiones sanitarias)

Dña. María Victoria Paricio Gómez (Enfermería)

Dr. José María Canelles Gamir (Farmacéutico de Atención Primaria)

Dr. Matteo Frasson (Cirugía General y Aparato Digestivo)

Dr. José Vicente Solanas Prats (Atención Primaria)

Dr. Óscar Díaz Cambrón (Anestesiología y Reanimación)

Dr. Javier Lluna González (Cirugía Pediátrica - Miembro del Comité de Ética Asistencial - Formación acreditada en Bioética)

D. Miguel Ángel Cano Torres (Secretario de ASLEUVAL - Miembro Lego - Ajeno a las profesiones sanitarias)

D. Vicente Inglada Alcaide (Secretario Unión de Consumidores de Valencia - Miembro ajeno a las profesiones sanitarias)

D. Antonio Juan Orduña Galán (Experto en Protección de Datos)

CONSENTIMIENTO POR ESCRITO

Título del estudio: Cerclaje en cervix incompetente diagnosticado por exploración física durante el 2º trimestre

Yo, _____ (nombre y apellidos).

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: _____ (nombre del Investigador)
- Comprendo que mi participación es voluntaria.
- Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Comprendo que puedo retirarme del estudio:

- 1º Cuando quiera
- 2º Sin tener que dar explicaciones.
- 3º Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio.

Firma del Participante

Nombre: _____

Fecha: ____/____/____

Firma del Investigador

Nombre: _____

Fecha: ____/____/____

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para mí salud: ☐ **Sí** ☐ **No**

Firma del representante _____ Fecha: ____/____/____ (Nombre, firma y fecha de puño y letra del representante legal)

Firma del investigador: _____ Fecha: ____/____/____

Deseo que me comuniquen la información derivada de las pruebas genéticas realizadas (únicamente para aquellos estudios que incluyan este tipo de pruebas, siempre que estén validadas y que puedan tener relevancia para la salud del paciente): ☐ **Sí** ☐ **No**

Firma del representante _____ Fecha: ____/____/____ (Nombre, firma y fecha de puño y letra del representante legal)

Firma del investigador: _____ Fecha: ____/____/____

CONSENTIMIENTO DEL REPRESENTANTE LEGAL

Título del estudio: Cerclaje en cervix incompetente diagnosticado por exploración física durante el 2º trimestre

Yo, _____ (nombre y apellidos)

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.

He hablado con: _____ (nombre del Investigador)

Comprendo que la participación de _____ (nombre del participante) es voluntaria.

Comprendo que _____ (nombre del participante) puede retirarse del estudio:

- 1º Cuando quiera
- 2º Sin tener que dar explicaciones.
- 3º Sin que esto repercuta en sus cuidados médicos.

En mi presencia se ha dado a _____ (nombre del participante), toda la información pertinente adaptada a su nivel de entendimiento y está de acuerdo en participar.

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

Y presto mi conformidad con que _____ (nombre del participante) participe en el estudio.

Firma del Representante

Firma del Investigador

Nombre: _____

Fecha: ____/____/____

Nombre: _____

Fecha: ____/____/____

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para mí salud: ☐ **Sí** ☐ **No**

Firma del representante _____ Fecha: ____/____/____ (Nombre, firma y fecha de puño y letra del representante legal)

Firma del investigador: _____ Fecha: ____/____/____

Deseo que me comuniquen la información derivada de las pruebas genéticas realizadas (únicamente para aquellos estudios que incluyan este tipo de pruebas, siempre que estén validadas y que puedan tener relevancia para la salud del paciente): ☐ **Sí** ☐ **No**

Firma del representante _____ Fecha: ____/____/____ (Nombre, firma y fecha de puño y letra del representante legal)

Firma del investigador: _____ Fecha: ____/____/____