

Recomendaciones para el manejo del aborto recurrente (AR)

Grupo de Trabajo de Fracaso Reproductivo



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De acuerdo al último consenso establecido por diversas sociedades médicas internacionales relacionadas con la reproducción, se acepta como definición de aborto recurrente (AR) la pérdida de dos o más gestaciones clínicas antes de la semana 22 de embarazo, pues a partir de esta edad gestacional hay descritos recién nacidos vivos. No se considera necesario que las pérdidas sean consecutivas pues la existencia de una causa de base que aumente la probabilidad de aborto no siempre conduce a éste.

En este documento se van a desarrollar las recomendaciones específicas para el diagnóstico y tratamiento del AR, que se añadirían a las aconsejadas preconceptionalmente a cualquier mujer que deseara gestar de forma espontánea o asistida, tales como la promoción de hábitos de vida saludables, la toma de ácido fólico y la realización de un estudio analítico sanguíneo básico que incluyese hemograma, hemostasia, bioquímica y determinación de TSH, además de otras posibles evaluaciones relacionadas con cualquier condición patológica que presentase la paciente. La realización de una anamnesis detallada sería también fundamental.

En esta guía de recomendaciones se presentan las causas investigadas de acuerdo a la fortaleza del **grado de recomendación**, de la siguiente forma: (*Eccles, Clapp et al. 1996*).

- A. basado en evidencia científica buena y consistente.
- B. basado en evidencia científica limitada (*o extrapolaciones de trabajos con nivel I de evidencia*).
- C. basado en consensos u opiniones de expertos (*o extrapolaciones de trabajos con niveles de evidencia II*).

En la estimación *a priori* del riesgo de un nuevo aborto en una paciente con AR los factores pronósticos más importantes son la edad femenina y el número de abortos previos. Según estos dos parámetros se podrá establecer la probabilidad de volver a abortar con el fin de que el médico y la paciente/pareja puedan consensuar el protocolo a seguir.

1. INVESTIGACIÓN Y MANEJO DE LA CAUSA GENÉTICA

- a. **Cariotipos paternos:** aunque la alteración de los cariotipos paternos sólo explica entre el 3 y el 5 % de los casos de AR, su coste-efectividad ha sido avalada en algunos estudios. **Grado B.**
- b. **Cariotipo de restos abortivos:** es recomendable realizar el cariotipo de los productos de la concepción con una técnica fiable para evitar la contaminación materna. Las técnicas de elección son la biopsia corial o la histeroembrioscopia previas al legrado convencional o el uso de técnicas moleculares en sangre materna y en los restos abortivos post-legrado. Para el adecuado estudio de una posible aneuploidía recurrente, sería recomendable dicho cariotipado ya desde el segundo aborto. **Grado B.**
- c. **Cribado genético preimplantacional (PGT-A):** cumple un doble objetivo: servir de diagnóstico del origen del aborto en caso de cromosomopatía y también de tratamiento al reducir la probabilidad de un nuevo aborto mediante la selección de embriones euploides para transferir. Su uso es controvertido al no existir en mujeres con AR estudios aleatorizados que hayan demostrado la mejora de los resultados reproductivos. Sin embargo, grupos con experiencia han mostrado reducir a menos de 10-15% la probabilidad de un nuevo aborto en mujeres con un riesgo *a priori* establecido entre un 30 y un 70% (según edad). Aunque no aumenta la tasa acumulada de recién nacido por ciclo de fecundación *in vitro*, sí acorta el tiempo hasta conseguir un embarazo evolutivo y parece resultar coste-efectivo. **Grado B.**

Por tanto, ante un caso de AR por aneuploidía recurrente demostrada o de AR idiopático (que frecuentemente es por aneuploidía recurrente), y considerando que la edad materna avanzada aumenta el riesgo de aborto y que ciertos tipos de infertilidad también se relacionan con problemas cromosómicos, se recomienda el PGT-A:

- Con dos o más abortos en pacientes \geq de 35 años
 - Con tres o más abortos en menores de 35 años.
 - Con dos o más abortos en pacientes menores de 35 años con infertilidad asociada.
- d. **Test no recomendados:** (por evidencia muy débil de su relación con el AR).
 - FISH de espermatozoides
 - Test de fragmentación del ADN
 - Realización de perfiles genéticos de mutaciones supuestamente ligadas al AR.

2. INVESTIGACIÓN Y MANEJO DE LAS TROMBOFILIAS

a. Trombofilias adquiridas

• Síndrome antifosfolípido (SAF)

1. Para el correcto diagnóstico del síndrome antifosfolípido, se debe realizar el mismo de una manera exhaustiva, cumpliendo un criterio clínico y un criterio analítico. Si bien en principio los criterios clínicos enunciados por Miyakis hacían referencia en el caso del aborto a la pérdida de al menos 3 gestaciones consecutivas antes de la semana 10 de embarazo o al menos una muerte fetal inexplicada de 10 o más semanas, se podría considerar su estudio a partir de dos pérdidas clínicas de cualquier edad gestacional en base a la definición actual de AR. **Grado A.**
2. Se harán las siguientes determinaciones analíticas, siguiendo los criterios expuestos en el protocolo diagnóstico (dos determinaciones positivas separadas al menos 12 semanas, en títulos moderados o elevados para los anticuerpos):
 - a. Ac anticardiolipina (ACA) IgG y/o IgM. **Grado A.**
 - c. Ac anti β 2 glicoproteína I IgG y/o IgM. **Grado A.**
 - d. Anticoagulante lúpico (AL). **Grado A.**

b. Trombofilias heredadas

Se podrían analizar las siguientes:

1. Mutación del factor V de Leiden. **Grado B.**
2. Mutación 20210A del gen del factor II. **Grado B.**

al ser las únicas que han mostrado cierta asociación con el AR en diversos estudios que incluyen revisiones sistemáticas y meta-análisis. Sin embargo, no existe acuerdo al respecto.

La intervención con terapias anticoagulantes en mujeres con AR y trombofilia heredada, fundamentalmente mediante administración de heparina, no ha sido evaluada en ningún ensayo aleatorizado bien diseñado hasta el momento actual. Según la última revisión Cochrane, se necesitan más estudios para aclarar este punto.

Para el tratamiento del SAF se recomienda el uso de ácido acetil salicílico a bajas dosis (75-100 mg diarios) y el uso de heparina, actualmente de bajo peso molecular, a dosis profilácticas. En recientes recomendaciones internacionales, se aconseja el uso de esta combinación para mujeres con SAF que han tenido al menos tres abortos clínicos, pues en estos casos ha mostrado aumentar la probabilidad de recién nacido vivo.

En ausencia de trombofilia, congénita o adquirida, la aspirina y/o heparina no han demostrado ningún efecto beneficioso, no recomendándose por tanto su uso.

En cualquier caso, siempre que se diagnostica una trombofilia es conveniente ponerlo en conocimiento del hematólogo para el manejo conjunto de la paciente.

3. INVESTIGACIÓN Y MANEJO DE LAS CAUSAS ALOINMUNES Y OTRAS AUTOINMUNES. **Grado B.**

Dado que no hay marcadores de aloinmunidad claramente relacionados (o con valor pronóstico) en el AR, y que no hay ninguna terapia inmunológica en la actualidad que haya demostrado aumentar la probabilidad de recién nacido en estas pacientes,

- **Determinación de KIR:** se considera que podría ser útil cuando se haya descartado cualquier otra causa incluyendo la embrionaria, es decir, cuando se producen abortos teniendo constancia que los embriones son euploides. En la actualidad se encuentra dentro del campo de la investigación.
- **Determinación de anticuerpos antitransglutaminasa (aTG):** si existe sospecha de enfermedad celíaca, bien porque se dan síntomas claros de la misma o sugestivos de la variedad paucisintomática, como la anemia ferropénica que no se corrige con ferrotterapia o un aumento idiopático de las transaminasas, tendría sentido la determinación de este anticuerpo, al ser barata y permitir el diagnóstico de certeza de la enfermedad con otras técnicas (biopsia intestinal). La celiaquía sin tratar podría aumentar el riesgo de aborto, y con una intervención tan sencilla como la retirada del gluten de la dieta dicho riesgo se eliminaría.
- **Determinación de los niveles de vitamina D:** no se considera recomendado, dado que no se ha encontrado una asociación clara con el AR, ni los suplementos con vitamina D han demostrado mejorar el pronóstico reproductivo de las pacientes abortadoras.
- **Otras determinaciones:** no se recomiendan, por no existir evidencia de asociación con el AR ni mejora en el pronóstico reproductivo con la determinación de marcadores tales como anticuerpos antinucleares (ANA), células NK uterinas, células NK periféricas, anticuerpos antipaternales o anticuerpos anti HY.

4. INVESTIGACIÓN Y MANEJO DE LAS CAUSAS ANATÓMICAS.

La recomendación para el estudio de las causas anatómicas es la realización de pruebas de imagen, preferiblemente la ecografía 3D, **Grado A** utilizando la histeroscopia tanto como método diagnóstico complementario, como terapéutico cuando se constata un problema anatómico.

Una vez realizado el diagnóstico, se recomienda intervenir las patologías que han sido relacionadas con el AR. Otras han sido únicamente asociadas con aborto esporádico o con la infertilidad (sinequias, pólipos, adenomiosis):

a. Malformaciones uterinas

- Úteros septos y subseptos
- Úteros hipoplásicos y úteros en T

Son las patologías que han presentado mayor asociación con la ocurrencia de AR, de las que hay más datos sobre la mejora del pronóstico reproductivo tras su corrección y que presentan una buena relación beneficio/riesgo en manos expertas, aunque no existe ningún estudio aleatorizado hasta el momento que haya demostrado la mejora en las tasas de recién nacido vivo tras su corrección en mujeres con AR. Se tratarían mediante cirugía histeroscópica. **Grado B.**

b. Miomas

Se considerará la intervención de aquellos miomas que tengan una localización submucosa, o los de localización intramural que por su situación o tamaño (normalmente mayores de 4 cm) resulten deformantes de la cavidad uterina. **Grado B.**

En este caso se utilizará la vía histeroscópica y/o laparoscópica para su resolución en función del tamaño y localización de los mismos.

c. Insuficiencia cervical

En los casos de AR de 2º trimestre por insuficiencia cervical, el cerclaje terapéutico parece eficaz para el alargamiento de la gestación cuando el cérvix por ecografía transvaginal se reduce a menos de 25 mm antes de la semana 24 de gestación en gestaciones únicas. **Grado B.**

La administración de progesterona también puede ser beneficiosa en estos casos.

5. INVESTIGACIÓN Y MANEJO DE LAS CAUSAS ENDOCRINAS.

a. Diabetes Mellitus

No se considera indicada la determinación de la glucemia en el contexto de la investigación de las causas de AR, dado que una diabetes subclínica o bien controlada no se ha asociado a un mayor riesgo de pérdida gestacional. La determinación de una glucemia basal estaría recomendada, como se apuntó, en el contexto de la evaluación preconcepcional de cualquier mujer con deseo gestacional.

b. Enfermedad tiroidea

Del mismo modo que la diabetes mellitus, una enfermedad tiroidea subclínica o bien controlada no supone un factor de riesgo de AR.

Se recomienda la determinación de la TSH en el contexto de la evaluación preconcepcional de la paciente, y en los casos en los que los valores sean superiores a 2.5 mUI/L, se solicitarán los anticuerpos antiperoxidada (antiTPO), dado que se estima que la presencia de estos anticuerpos puede ser un factor acelerador de una patología tiroidea larvada, en cuyo caso se recomendaría el tratamiento con Levotiroxina. La evaluación y seguimiento por un endocrinólogo es altamente aconsejable en estas pacientes.

c. Síndrome de ovario poliquístico (SOP).

Dada la falta de asociación del SOP con el AR, no se considera indicada ninguna investigación en este sentido. La administración de metformina tampoco ha demostrado reducir la probabilidad de aborto en las mujeres afectas.

d. Insuficiencia de CL

El diagnóstico de la insuficiencia de cuerpo lúteo es altamente impreciso y subjetivo y la administración de progesterona vaginal micronizada en mujeres abortadoras idiopáticas desde el momento en

que conocen que están embarazadas no ha demostrado aumentar la probabilidad de recién nacido en base a un estudio aleatorizado reciente. Por ello, no hay evidencia actual para su administración en el AR, salvo en el contexto del cuidado emocional de la paciente o *tender loving care*, medida que sí parece mejorar el pronóstico reproductivo de las pacientes con AR. Quizá otras presentaciones de progesterona (parenteral) o un inicio más temprano de la misma (fase lútea) pudieran jugar un papel en la mejora del pronóstico reproductivo en caso de AR, aunque se necesitan más estudios para determinarlo.

e. Hiperprolactinemia

No se considera indicada su determinación, dada la ausencia de relación con el AR. En el caso de las pacientes infértiles y en el contexto de la evaluación preconcepcional se recomienda la determinación de PRL.

6. INVESTIGACIÓN DE LAS CAUSAS INFECCIOSAS.

Dado que no existe evidencia de que estén relacionadas con el AR, no se considera su investigación.

7. INVESTIGACIÓN Y MANEJO DE LAS CAUSAS RELACIONADAS CON EL ESTILO DE VIDA.

No existe evidencia clara de que los hábitos no saludables, el sobrepeso o la exposición a tóxicos estén relacionados con la ocurrencia de AR. En cualquier caso, es sensato recomendar todos aquellos hábitos saludables que pueden contribuir a la mejora de otros aspectos de la salud o del embarazo de la paciente, pudiendo también tener un efecto placebo dentro del marco del cuidado emocional intensivo del inicio del embarazo o *tender loving care* de la paciente abortadora de repetición.

8. OTRAS CONSIDERACIONES.

- a. Se recomienda en las mujeres con AR, tanto idiopático como con causa conocida, el cuidado emocional intensivo del inicio del embarazo, pues parece mejorar la probabilidad de embarazo evolutivo, quizá por reducción de mecanismos deletéreos estrés-dependientes. **Grado C**
- b. Del mismo modo, es aconsejable el control de estas pacientes en unidades de embarazo de alto riesgo una vez conciban, pues incluso en los casos idiopáticos se ha descrito una mayor incidencia de complicaciones gestacionales. **Grado B.**
- c. En mujeres que sigan abortando pese a las medidas antes expuestas, se les podrá recomendar la donación de gametos, el útero subrogado en países donde sea legal, o la adopción. **Grado A.**

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