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 preconcepcionalmente a cualquier mujer que desease 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 aneuplodía recurrente demostrada o de AR idiopático (que frecuentemente es por aneuplodía 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 ≥ 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 ß2 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 ferroterapia 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.**

Referencias bibliográficas para la elaboración del documento

- *Eccles M, Clapp Z, Grimshaw J, Adams PC, Higgins B, Purves I, et al. North of England evidence based guidelines development project: methods of guideline development. BMJ: British Medical Journal 1996;312:760.*
- *Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002;12(1):63-68.*
- *Abir R, Fisch B, Nahum R, Orvieto R, Nitke S, Ben Rafael Z. Turner's syndrome and fertility: Current status and possible putative prospects. Hum Reprod Update. 2001;7(6):603-610.*
- *Abulí A, Boada M, Rodríguez-Santiago B, et al. NGS-Based assay for the identification of individuals carrying recessive genetic mutations in reproductive medicine. Hum Mutat. 2016;37(6):516-523.*
- *Adams JS, Hewison M. Unexpected actions of vitamin D: New perspectives on the regulation of innate and adaptive immunity. Nature Reviews Endocrinology. 2008;4(2):80.*
- *Alecsandru D, Garrido N, Vicario JL, et al. Maternal KIR haplotype influences live birth rate after double embryo transfer in IVF cycles in patients with recurrent miscarriages and implantation failure. Human reproduction. 2014;29(12):2637-2643.*
- *Alfarawati S, Fragouli E, Colls P, et al. The relationship between blastocyst morphology, chromosomal abnormality, and embryo gender. Fertil Steril. 2011;95(2):520-524.*
- *Andersen AN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: Population based register linkage study. BMJ. 2000;320(7251):1708-1712.*
- *Andraweera PH, Dekker GA, Jayasekara RW, Dissanayake VH, Roberts CT. The obesity-related FTO gene variant associates with the risk of recurrent miscarriage. Acta Obstet Gynecol Scand. 2015;94(7):722-726.*
- *Aran B, Veiga A, Vidal F, et al. Preimplantation genetic diagnosis in patients with male meiotic abnormalities. Reproductive biomedicine online. 2004;8(4):470-476.*
- *Arredondo F, Noble LS. Endocrinology of recurrent pregnancy loss. . 2006;24(01):33.*
- *Arslan AA, Gold LI, Mittal K, et al. Gene expression studies provide clues to the pathogenesis of uterine leiomyoma: New evidence and a systematic review. Human reproduction. 2005;20(4):852-863.*
- *Azimi M, Schmaus K, Greger V, Neitzel D, Rochelle R, Dinh T. Carrier screening by next-generation sequencing: Health benefits and cost effectiveness. Molecular genetics & genomic medicine. 2016;4(3):292-302.*
- *Bai JC, Fried M, Corazza GR, et al. World gastroenterology organisation global guidelines on celiac disease. J Clin Gastroenterol. 2013;47(2):121-126.*
- *Bakalov VK, Shawker T, Ceniceros I, Bondy CA. Uterine development in turner syndrome. J Pediatr. 2007;151(5):531. e1.*
- *Banzato PCA, Daher S, Traina v, et al. FAS and FAS-L genotype and expression in patients with recurrent pregnancy loss. Reproductive Sciences. 2013;20(9):1111-1115.*
- *Barratt CL, Aitken RJ, Björndahl L, et al. Sperm DNA: Organization, protection and vulnerability: From basic science to clinical applications—a position report. Human reproduction. 2010;25(4):824-838.*
- *Baudat F, Imai Y, De Massy B. Meiotic recombination in mammals: Localization and regulation. Nature Reviews.Genetics. 2013;14(11):794.*
- *Bellver J, Soares SR, Alvarez C, et al. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Hum Reprod. 2008;23(2):278-284.*
- *Bellver J, Cruz F, Martínez MC, et al. Female overweight is not associated with a higher embryo euploidy rate in first trimester miscarriages karyotyped by hysteroembryoscopy. Fertil Steril. 2011;96(4):933. e1.*
- *Bellver J, Martínez-Conejero JA, Labarta E, et al. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. Fertil Steril. 2011;95(7):2341. e8.*
- *Bellver J, Pellicer A, García-Velasco JA, Ballesteros A, Remohí J, Meseguer M. Obesity reduces uterine receptivity: Clinical experience from 9,587 first cycles of ovum donation with normal weight donors. Fertil Steril. 2013;100(4):1058. e2.*
- *Ben-Nagi J, Miell J, Yazbek J, Holland T, Jurkovic D. The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings. Reproductive biomedicine online. 2009;19(5):737-744.*
- *Beniada A, Benoist G, Maurel J, Dreyfus M. Inflammatory bowel disease and pregnancy: Report of 76 cases and review of the literature. J Gynecol Obstet Biol Reprod. 2005;34(6):581-588.*
- *Benkhalifa M, Kasakyan S, Clement P, et al. Array comparative genomic hybridization profiling of first-trimester spontaneous abortions that fail to grow in vitro. Prenat Diagn. 2005;25(10):894-900.*
- *Berghella V. Novel developments on cervical length screening and progesterone for preventing preterm birth. BJOG: An International Journal of Obstetrics & Gynaecology. 2009;116(2):182-187.*
- *Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: A meta-analysis. Obstetrics & Gynecology. 2011;117(3):663-671.*

- *Bermas BL, Sammaritano LR. Fertility and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Fertility research and practice. 2015;1(1):13.*
- *Bermas BL, Sammaritano LR. Fertility and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Fertility research and practice. 2015;1(1):13.*
- *Bernard V, Donadille B, Zenaty D, et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with turner syndrome. Human Reproduction. 2016;31(4):782-788.*
- *Bernardi LA, Cohen RN, Stephenson MD. Impact of subclinical hypothyroidism in women with recurrent early pregnancy loss. Fertil Steril. 2013;100(5):1331. e1.*
- *Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369(6475):64.*
- *Bhandari HM, Tan BK, Quenby S. Superfertility is more prevalent in obese women with recurrent early pregnancy miscarriage. BJOG: An International Journal of Obstetrics & Gynaecology. 2016;123(2):217-222.*
- *Bianco K, Caughey AB, Shaffer BL, Davis R, Norton ME. History of miscarriage and increased incidence of fetal aneuploidy in subsequent pregnancy. Obstetrics & Gynecology. 2006;107(5):1098-1102.*
- *Boots CE, Bernardi LA, Stephenson MD. Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. Fertil Steril. 2014;102(2):455-459.*
- *Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: A systematic review. . 2011;29(06):507-513.*
- *Bosteels J, Weyers S, Puttemans P, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: A systematic review. Hum Reprod Update. 2009;16(1):1-11.*
- *Bovill EG, Hasstedt SJ, Leppert MF, Long GL. Hereditary thrombophilia as a model for multigenic disease. Thromb Haemost. 1999;82(02):662-666.*
- *Boyd HA, Basit S, Harpsøe MC, Wohlfahrt J, Jess T. Inflammatory bowel disease and risk of adverse pregnancy outcomes. PLoS One. 2015;10(6):e0129567.*
- *Brenner B, Sarig G, Weiner Z, Younis J, Blumenfeld Z, Lanir N. Thrombophilic polymorphisms are common in women with fetal loss without apparent cause. Thromb Haemost. 1999;82(01):6-9.*
- *Brenner B, Mandel H, Lanir N, et al. Activated protein C resistance can be associated with recurrent fetal loss. Br J Haematol. 1997;97(3):551-554.*
- *Brezina PR, Kearns WG. The evolving role of genetics in reproductive medicine. Obstet Gynecol Clin North Am. 2014;41(1):41-55.*
- *Brezina PR, Kutteh WH. Recurrent early pregnancy loss. In: Clinical reproductive medicine and surgery. Springer; 2017:269-288.*
- *Brucker SY, Rall K, Campo R, Oppelt P, Isaacson K. Treatment of congenital malformations. . 2011;29(02):101-112.*
- *Burrello N, Vicari E, Shin P, et al. Lower sperm aneuploidy frequency is associated with high pregnancy rates in ICSI programmes. Human Reproduction. 2003;18(7):1371-1376.*
- *Bussen S, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. Hum Reprod. 1995;10(11):2938-2940.*
- *Capalbo A, Bono S, Spizzichino L, et al. Sequential comprehensive chromosome analysis on polar bodies, blastomeres and trophoblast: Insights into female meiotic errors and chromosomal segregation in the preimplantation window of embryo development. Human Reproduction. 2012;28(2):509-518.*
- *Carp HJ. Recurrent miscarriage: Genetic factors and assessment of the embryo. IMAJ. 2008;10(3):229-231.*
- *Carp H, Toder V, Aviram A, Daniely M, Mashiach S, Barkai G. Karyotype of the abortus in recurrent miscarriage. Fertil Steril. 2001;75(4):678-682.*
- *Caseiro AL, Regalo A, Pereira E, Esteves T, Fernandes F, Carvalho J. Implication of sperm chromosomal abnormalities in recurrent abortion and multiple implantation failure. Reproductive biomedicine online. 2015;31(4):481-485.*
- *Cerezo CA, Glvez MCC, de la Fuente Hernndez, Luis Alfonso, et al. Recomendaciones para el estudio gentico de la pareja con alteraciones en la reproduccin. Revista del Laboratorio Clnico. 2009;2(4):196-203.*
- *Chakraborty P, Goswami SK, Rajani S, et al. Recurrent pregnancy loss in polycystic ovary syndrome: Role of hyperhomocysteinemia and insulin resistance. PLoS One. 2013;8(5):e64446.*
- *Chan WP, Lee CK, Kwong YL, Lam CK, Liang R. A novel mutation of Arg306 of factor V gene in hong kong chinese. Blood. 1998;91(4):1135-1139.*
- *Chen L, Hu R. Thyroid autoimmunity and miscarriage: A meta-analysis. Clin Endocrinol (Oxf). 2011;74(4):513-519.*
- *Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1, 25-dihydroxyvitamin D3 on human B cell differentiation. The Journal of Immunology. 2007;179(3):1634-1647.*
- *Choi TY, Lee HM, Park WK, Jeong SY, Moon HS. Spontaneous abortion and recurrent miscarriage: A comparison of cytogenetic diagnosis in 250 cases. Obstetrics & gynecology science. 2014;57(6):518-525.*

- *Christakos S, DeLuca HF. Minireview: Vitamin D: Is there a role in extraskeletal health? Endocrinology. 2011;152(8):2930-2936.*
- *Christiansen OB, Andersen AN, Bosch E, et al. Evidence-based investigations and treatments of recurrent pregnancy loss. Fertil Steril. 2005;83(4):821-839.*
- *Christiansen OB, Mathiesen O, Lauritsen JG, Grunnet N. Idiopathic recurrent spontaneous abortion: Evidence of a familial predisposition. Acta Obstet Gynecol Scand. 1990;69(7-8):597-601.*
- *Ciarmatori S. Aborto recurrente de causa endocrina. Reproducción. 2012;27:138-159.*
- *Clifford K, Rai R, Watson H, Franks S, Regan L. Does suppressing luteinising hormone secretion reduce the miscarriage rate? results of a randomised controlled trial. BMJ. 1996;312(7045):1508-1511.*
- *Clifford K, Rai R, Watson H, Regan L. Pregnancy: An informative protocol for the investigation of recurrent miscarriage: Preliminary experience of 500 consecutive cases. Human reproduction. 1994;9(7):1328-1332.*
- *Clowse ME, Chakravarty E, Costenbader KH, Chambers C, Michaud K. Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis care & research. 2012;64(5):668-674.*
- *Cocksedge KA, Saravelos SH, Metwally M, Li TC. How common is polycystic ovary syndrome in recurrent miscarriage? Reproductive biomedicine online. 2009;19(4):572-576.*
- *Cocksedge KA, Li T, Saravelos SH, Metwally M. A reappraisal of the role of polycystic ovary syndrome in recurrent miscarriage. Reproductive biomedicine online. 2008;17(1):151-160.*
- *Comstock IA, Diaz-Gimeno P, Cabanillas S, et al. Does an increased body mass index affect endometrial gene expression patterns in infertile patients? A functional genomics analysis. Fertil Steril. 2017;107(3):748. e2.*
- *Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T, Pregnancy in Multiple Sclerosis Group. Rate of pregnancy-related relapse in multiple sclerosis. N Engl J Med. 1998;339(5):285-291.*
- *Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 2015;373(22):2141-2148.*
- *Correale J, Arias M, Gilmore W. Steroid hormone regulation of cytokine secretion by proteolipid protein-specific CD4 T cell clones isolated from multiple sclerosis patients and normal control subjects. The Journal of Immunology. 1998;161(7):3365-3374.*
- *Correale J, Farez MF, Ysrraelit MC. Increase in multiple sclerosis activity after assisted reproduction technology. Ann Neurol. 2012;72(5):682-694.*
- *Costa OLN, Santos EMF, Netto EM. Epidemiological and obstetrics aspects in women with recurrent pregnancy losses at a public maternity in the brazilian northeast. Revista Brasileira de Ginecologia e Obstetrícia. 2014;36(11):514-518.*
- *Craig LB, Ke RW, Kutteh WH. Increased prevalence of insulin resistance in women with a history of recurrent pregnancy loss. Fertil Steril. 2002;78(3):487-490.*
- *Crosignani PG. Genetic aspects of female reproduction. Hum Reprod Update. 2008;14(4).*
- *D'Ippolito S, Meroni PL, Koike T, Veglia M, Scambia G, Di Simone N. Obstetric antiphospholipid syndrome: A recent classification for an old defined disorder. Autoimmunity reviews. 2014;13(9):901-908.*
- *Danza A, Ruiz-Irastorza G, Khamashta M. Antiphospohlipid syndrome in obstetrics. Best practice & research Clinical obstetrics & gynaecology. 2012;26(1):65-76.*
- *Daya S, Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. Fertil Steril. 1996;66(1):24-29.*
- *De Jesus GR, Agmon-Levin N, Andrade CA, et al. 14th international congress on antiphospholipid antibodies task force report on obstetric antiphospholipid syndrome. Autoimmunity reviews. 2014;13(8):795-813.*
- *De Vivo A, Mancuso A, Giacobbe A, et al. Thyroid function in women found to have early pregnancy loss. Thyroid. 2010;20(6):633-637.*
- *Devine DH, Whitman-Elia G, Best RG, Edwards JG. Paternal paracentric inversion of chromosome 2: A possible association with recurrent pregnancy loss and infertility. J Assist Reprod Genet. 2000;17(5):293-296.*
- *Di Simone N, Meroni PL, D'Asta M, Di Nicuolo F, D'Alessio MC, Caruso A. Pathogenic role of anti-β2-glycoprotein I antibodies on human placenta: Functional effects related to implantation and roles of heparin. Hum Reprod Update. 2006;13(2):189-196.*
- *Dossenbach-Glaninger A, van Trotsenburg M, Krugluger W, et al. Elevated coagulation factor VIII and the risk for recurrent early pregnancy loss. Thromb Haemost. 2004;92(04):694-699.*
- *Doğer E, Çakıroğlu Y, Ceylan Y, Ulak E, Özdamar Ö, Çalışkan E. Reproductive and obstetric outcomes in mosaic turner's syndrome: A cross-sectional study and review of the literature. Reproductive Biology and Endocrinology. 2015;13(1):59.*
- *Dutta UR, Rajitha P, Pidugu VK, Dalal AB. Cytogenetic abnormalities in 1162 couples with recurrent miscarriages in southern region of india: Report and review. J Assist Reprod Genet. 2011;28(2):145-149.*
- *Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ. Early embryonic mortality in women. Fertil Steril. 1982;38(4):447-453.*
- *Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine—points to consider: A joint statement of the american college of medical genetics and genomics, american college of obstetricians and gynecologists, natio-*

nal society of genetic counselors, perinatal quality foundation, and society for maternal-fetal medicine. Obstetrics & Gynecology. 2015;125(3):653-662.

- *Egozcue S, Blanco J, Vendrell JM, et al. Human male infertility: Chromosome anomalies, meiotic disorders, abnormal spermatozoa and recurrent abortion. Hum Reprod Update. 2000;6(1):93-105.*
- *Eiben B, Bartels I, Bhr-Porsch S, et al. Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. Am J Hum Genet. 1990;47(4):656.*
- *El-Hamarneh T, Hey-Cunningham AJ, Berbic M, Al-Jefout M, Fraser IS, Black K. Cellular immune environment in endometrial polyps. Fertil Steril. 2013;100(5):1364-1372.*
- *ESHRE Capri Workshop Group. Genetic aspects of female reproduction. Hum Reprod Update. 2008;14(4):293-307.*
- *Esplin MS, Branch DW, Silver R, Stagnaro-Green A. Thyroid autoantibodies are not associated with recurrent pregnancy loss. Obstet Gynecol. 1998;179(6):1583-1586.*
- *Evenson D, Jost L. Sperm chromatin structure assay is useful for fertility assessment. Methods in Cell Science. 2000;22(2):169-189.*
- *Faridi RM, Agrawal S. Killer immunoglobulin-like receptors (KIRs) and HLA-C allorecognition patterns implicative of dominant activation of natural killer cells contribute to recurrent miscarriages. Human reproduction. 2010;26(2):491-497.*
- *Fedele L, Bianchi S, Marchini M, Mezzopane R, Nola GD, Tozzi L. Residual uterine septum of less than 1 cm after hysteroscopic metroplasty does not impair reproductive outcome. Human Reproduction. 1996;11(4):727-729.*
- *Ferro J, Martnez MC, Lara C, Pellicer A, Remoh J, Serra V. Improved accuracy of hysteroembryoscopic biopsies for karyotyping early missed abortions. Fertil Steril. 2003;80(5):1260-1264.*
- *Finan RR, Tamim H, Ameen G, Sharida HE, Rashid M, Almawi WY. Prevalence of factor V G1691A (factor V-Leiden) and prothrombin G20210A gene mutations in a recurrent miscarriage population. Am J Hematol. 2002;71(4):300-305.*
- *Fischer-Betz R, Specker C. Pregnancy in systemic lupus erythematosus and antiphospholipid syndrome. Best Practice & Research Clinical Rheumatology. 2017;31(3):397-414.*
- *Fishel S, Baker D, Elson J, et al. Precision medicine in assisted conception: A multicenter observational treatment cohort study of the annexin A5 M2 haplotype as a biomarker for antithrombotic treatment to improve pregnancy outcome. EBioMedicine. 2016;10:298-304.*
- *Foka ZJ, Lambropoulos AF, Saravelos H, et al. Factor V leiden and prothrombin G20210A mutations, but not methylenetetrahydrofolate reductase C677T, are associated with recurrent miscarriages. Human Reproduction. 2000;15(2):458-462.*
- *Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007;357(5):462-469.*
- *Fox NS, Chervenak FA. Cervical cerclage: A review of the evidence. Obstet Gynecol Surv. 2008;63(1):58-65.*
- *Fraga LR, Dutra CG, Boquett JA, et al. P53 signaling pathway polymorphisms associated to recurrent pregnancy loss. Mol Biol Rep. 2014;41(3):1871-1877.*
- *Franssen MT, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: Case-control study. BMJ. 2006;332(7544):759-763.*
- *Galliano D, Bellver J, Díaz-García C, Simón C, Pellicer A. ART and uterine pathology: How relevant is the maternal side for implantation? Hum Reprod Update. 2014;21(1):13-38.*
- *Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the american association of clinical endocrinologists and the american thyroid association. Thyroid. 2012;22(12):1200-1235.*
- *Garrido N, Bellver J, Remohí J, Simón C, Pellicer A. Cumulative live-birth rates per total number of embryos needed to reach newborn in consecutive in vitro fertilization (IVF) cycles: A new approach to measuring the likelihood of IVF success. Fertil Steril. 2011;96(1):40-46.*
- *Garrisi JG, Colls P, Ferry KM, Zheng X, Garrisi MG, Munn S. Effect of infertility, maternal age, and number of previous miscarriages on the outcome of preimplantation genetic diagnosis for idiopathic recurrent pregnancy loss. Fertil Steril. 2009;92(1):288-295.*
- *Gasbarrini A, Torre ES, Trivellini C, De Carolis S, Caruso A, Gasbarrini G. Recurrent spontaneous abortion and intrauterine fetal growth retardation as symptoms of coeliac disease. The Lancet. 2000;356(9227):399-400.*
- *Geraedts J. Chromosomal anomalies and recurrent miscarriage. INFERTILITY AND REPRODUCTIVE MEDICINE CLINICS OF NORTH AMERICA. 1996;7:677-688.*
- *Gilmore W, Weiner LP, Correale J. Effect of estradiol on cytokine secretion by proteolipid protein-specific T cell clones isolated from multiple sclerosis patients and normal control subjects. The Journal of Immunology. 1997;158(1):446-451.*
- *Glueck CJ, Sieve L, Zhu B, Wang P. Plasminogen activator inhibitor activity, 4G5G polymorphism of the plasminogen activator inhibitor 1 gene, and first-trimester miscarriage in women with polycystic ovary syndrome. Metab Clin Exp. 2006;55(3):345-352.*
- *Goddijn M, Leschot NJ. Genetic aspects of miscarriage. Best Practice & Research Clinical Obstetrics & Gynaecology. 2000;14(5):855-865.*

- *Goldman KN, Hodes-Wertz B, McCulloh DH, Flom JD, Grifo JA. Association of body mass index with embryonic aneuploidy. Fertil Steril. 2015;103(3):744-748.*
- *GOLDSTEIN P, BERRIER J, ROSEN S, SACKS HS, CHALMERS TC. A meta-analysis of randomized control trials of progestational agents in pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology. 1989;96(3):265-274.*
- *Grandone E, Margaglione M, Colaizzo D, et al. Factor V leiden is associated with repeated and recurrent unexplained fetal losses. Thromb Haemost. 1997;77(05):822.*
- *Greco E, Romano S, Iacobelli M, et al. ICSI in cases of sperm DNA damage: Beneficial effect of oral antioxidant treatment. Human Reproduction. 2005;20(9):2590-2594.*
- *Greco L, Veneziano A, Di Donato L, et al. Undiagnosed coeliac disease does not appear to be associated with unfavourable outcome of pregnancy. Gut. 2004;53(1):149-151.*
- *Gris J, Quéré I, Monpeyrou F, et al. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent. Thromb Haemost. 1999;82(06):891-899.*
- *Gris J, Ripart-Neveu S, Maugard C, et al. Prospective evaluation of the prevalence of haemostasis abnormalities in unexplained primary early recurrent miscarriages. Thromb Haemost. 1997;77(06):1096-1103.*
- *Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Obstet Gynecol Surv. 2013;68(12):785-787.*
- *Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev. 2008;2:CD003511.*
- *Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database of Systematic Reviews. 2013(10).*
- *Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: A systematic review and meta-analysis. Hum Reprod Update. 2013;19(4):330-353.*
- *Hardy K, Hardy PJ. 1st trimester miscarriage: Four decades of study. Translational pediatrics. 2015;4(2):189.*
- *Harpham ME, Algert CS, Roberts CL, Ford JB, Shand AW. Cervical cerclage placed before 14 weeks gestation in women with one previous midtrimester loss: A population-based cohort study. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;57(6):593-598.*
- *Harton G, Braude P, Lashwood A, et al. ESHRE PGD consortium best practice guidelines for organization of a PGD centre for PGD/preimplantation genetic screening. Human reproduction. 2011;26(1):14-24.*
- *Hassold TJ. A cytogenetic study of repeated spontaneous abortions. Am J Hum Genet. 1980;32(5):723.*
- *Hassold T, Warburton D, Kline J, Stein Z. The relationship of maternal age and trisomy among trisomic spontaneous abortions. Am J Hum Genet. 1984;36(6):1349.*
- *Hatasaka H. Clinical management of the uterine factor in infertility. Clin Obstet Gynecol. 2011;54(4):696-709.*
- *Hellwig K, Correale J. Artificial reproductive techniques in multiple sclerosis. Clinical Immunology. 2013;149(2):219-224.*
- *Henkel R, Hajimohammad M, Stalf T, et al. Influence of deoxyribonucleic acid damage on fertilization and pregnancy. Fertil Steril. 2004;81(4):965-972.*
- *Hiby SE, Regan L, Lo W, Farrell L, Carrington M, Moffett A. Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Human reproduction. 2008;23(4):972-976.*
- *Hiby SE, Apps R, Sharkey AM, et al. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. J Clin Invest. 2010;120(11):4102-4110.*
- *Hiby SE, Walker JJ, O'Shaughnessy KM, et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. J Exp Med. 2004;200(8):957-965.*
- *Hodes-Wertz B, Grifo J, Ghadir S, et al. Idiopathic recurrent miscarriage is caused mostly by aneuploid embryos. Fertil Steril. 2012;98(3):675-680.*
- *Hofmann GE, Khoury J, Thie J. Recurrent pregnancy loss and diminished ovarian reserve. Fertil Steril. 2000;74(6):1192-1195.*
- *Hogge WA, Byrnes AL, Lanasa MC, Surti U. The clinical use of karyotyping spontaneous abortions. Obstet Gynecol. 2003;189(2):397-400.*
- *Hollis BW, Wagner CL. Vitamin D supplementation during pregnancy: Improvements in birth outcomes and complications through direct genomic alteration. Mol Cell Endocrinol. 2017;453:113-130.*
- *Holubcov Z, Blayney M, Elder K, Schuh M. Error-prone chromosome-mediated spindle assembly favors chromosome segregation defects in human oocytes. Science. 2015;348(6239):1143-1147.*
- *Homer HA, Li T, Cooke ID. The septate uterus: A review of management and reproductive outcome. Fertil Steril. 2000;73(1):1-14.*
- *Hooker AB, Lemmers M, Thurkow AL, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: Prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013;20(2):262-278.*
- *Horcajadas JA, Pellicer A, Simon C. Wide genomic analysis of human endometrial receptivity: New times, new opportunities. Hum Reprod Update. 2006;13(1):77-86.*

- *Huchon C, Deffieux X, Beucher G, et al. No title. Pregnancy loss: French clinical practice guidelines. 2016.*
- *Hyde KJ, Schust DJ. Genetic considerations in recurrent pregnancy loss. Cold Spring Harbor perspectives in medicine. 2015;5(3):a023119.*
- *Ikuma S, Sato T, Sugiura-Ogasawara M, Nagayoshi M, Tanaka A, Takeda S. Preimplantation genetic diagnosis and natural conception: A comparison of live birth rates in patients with recurrent pregnancy loss associated with translocation. PloS one. 2015;10(6):e0129958.*
- *Israel R, Stern JJ, Dorfmann AD, Gutirrez-Najar AJ, Cerrillo M, Coulam CB. Frequency of abnormal karyotypes among abortuses from women with and without a history of recurrent spontaneous abortion. Fertil Steril. 1996;65(2):250-253.*
- *Jarrett KL, Michaelis RC, Phelan MC, Vincent VA, Best RG. Microsatellite analysis reveals a high incidence of maternal cell contamination in 46, XX products of conception consisting of villi or a combination of villi and membranous material. Obstet Gynecol. 2001;185(1):198-203.*
- *Jaslow CR. Uterine factors. Obstetrics and Gynecology Clinics. 2014;41(1):57-86.*
- *Jayaprakasan K, Chan YY, Sur S, Deb S, Clewes JS, Raine-Fenning NJ. Prevalence of uterine anomalies and their impact on early pregnancy in women conceiving after assisted reproduction treatment. Ultrasound in Obstetrics & Gynecology. 2011;37(6):727-732.*
- *Johnson NP, Stewart AW, Falkiner J, et al. PCOSMIC: A multi-centre randomized trial in women with PolyCystic ovary syndrome evaluating metformin for infertility with clomiphene. Human reproduction. 2010;25(7):1675-1683.*
- *Jones KT, Lane SI. Molecular causes of aneuploidy in mammalian eggs. Development. 2013;140(18):3719-3730.*
- *Jung SJ, Park SK, Shin A, et al. Body mass index at age 18–20 and later risk of spontaneous abortion in the health examinees study (HEXA). BMC pregnancy and childbirth. 2015;15(1):228.*
- *Kahraman S, Findikli N, Biricik A, et al. Preliminary FISH studies on spermatozoa and embryos in patients with variable degrees of teratozoospermia and a history of poor prognosis. Reproductive biomedicine online. 2006;12(6):752-761.*
- *Keenan K, Grundy E, Kenward MG, Leon DA. Women's risk of repeat abortions is strongly associated with alcohol consumption: A longitudinal analysis of a russian national panel study, 1994–2009. PloS one. 2014;9(3):e90356.*
- *Kingsmore S. Comprehensive carrier screening and molecular diagnostic testing for recessive childhood diseases. PLoS currents. 2012;4.*
- *Kohn TP, Kohn JR, Darilek S, Ramasamy R, Lipshultz L. Genetic counseling for men with recurrent pregnancy loss or recurrent implantation failure due to abnormal sperm chromosomal aneuploidy. J Assist Reprod Genet. 2016;33(5):571-576.*
- *Kolte AM, Olsen LR, Mikkelsen EM, Christiansen OB, Nielsen HS. Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss. Human Reproduction. 2015;30(4):777-782.*
- *Kroon B, Johnson N, Chapman M, Yazdani A, Roger H. Fibroids in infertility–consensus statement from ACCEPT (australasian CREI consensus expert panel on trial evidence). Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011;51(4):289-295.*
- *Kumar A, Meena M, Begum N, et al. Latent celiac disease in reproductive performance of women. Fertil Steril. 2011;95(3):922-927.*
- *Kumar K, Deka D, Singh A, Mitra DK, Vanitha BR, Dada R. Predictive value of DNA integrity analysis in idiopathic recurrent pregnancy loss following spontaneous conception. J Assist Reprod Genet. 2012;29(9):861-867.*
- *Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med. 1999;340(1):9-13.*
- *Kutteh WH, Yetman DL, Carr AC, Beck LA, Scott RT. Increased prevalence of antithyroid antibodies identified in women with recurrent pregnancy loss but not in women undergoing assisted reproduction. Fertil Steril. 1999;71(5):843-848.*
- *Lambert-Messerlian G, McClain M, Haddow JE, et al. First-and second-trimester thyroid hormone reference data in pregnant women: A FaSTER (first-and second-trimester evaluation of risk for aneuploidy) research consortium study. Obstet Gynecol. 2008;199(1):62. e6.*
- *Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. BMC medicine. 2013;11(1):154.*
- *Larson SA, Khaleghi S, Rubio-Tapia A, et al. Prevalence and morbidity of undiagnosed celiac disease from a community-based study. Gastroenterology. 2017;152(4):839. e5.*
- *Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: Matched case–control study. Human reproduction. 2004;19(7):1644-1646.*
- *Lathi RB, Milki AA. Tissue sampling technique affects accuracy of karyotype from missed abortions. J Assist Reprod Genet. 2002;19(11):536-538.*
- *LeBeau SO, Mandel SJ. Thyroid disorders during pregnancy. Endocrinol Metab Clin North Am. 2006;35(1):117-136.*
- *Legro RS, Barnhart HX, Schlaff WD, et al. Cooperative multicenter reproductive medicine network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome.N Engl J Med. 2007;356(6):551-566.*
- *Letterie GS. Management of congenital uterine abnormalities. Reproductive biomedicine online. 2011;23(1):40-52.*

- *Levi AJ, Raynault MF, Bergh PA, Drews MR, Miller BT, Scott RT. Reproductive outcome in patients with diminished ovarian reserve. Fertil Steril. 2001;76(4):666-669.*
- *Levy B, Sigurjonsson S, Pettersen B, et al. Genomic imbalance in products of conception: Single-nucleotide polymorphism chromosomal microarray analysis. Obstetrics & Gynecology. 2014;124(2, PART 1):202-209.*
- *Lewis NR, Scott BB. Systematic review: The use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Aliment Pharmacol Ther. 2006;24(1):47-54.*
- *Lewis SE, Aitken RJ, Conner SJ, et al. The impact of sperm DNA damage in assisted conception and beyond: Recent advances in diagnosis and treatment. Reproductive BioMedicine Online. 2013;27(4):325-337.*
- *Li TC, Makris M, Tomsu M, Tuckerman E, Laird S. Recurrent miscarriage: Aetiology, management and prognosis. Hum Reprod Update. 2002;8(5):463-481.*
- *Li TC, Spuijbroek MD, Tuckerman E, Anstie B, Loxley M, Laird S. Endocrinological and endometrial factors in recurrent miscarriage. BJOG: An International Journal of Obstetrics & Gynaecology. 2000;107(12):1471-1479.*
- *Li W, Newell-Price J, Jones GL, Ledger WL, Li TC. Relationship between psychological stress and recurrent miscarriage. Reproductive biomedicine online. 2012;25(2):180-189.*
- *Liddell HS, Sowden K, Farquhar CM. Recurrent miscarriage: Screening for polycystic ovaries and subsequent pregnancy outcome. Australian and New Zealand journal of obstetrics and gynaecology. 1997;37(4):402-406.*
- *Lie RT, Lyngstadass A, rstavik KH, Bakketeig LS, Jacobsen G, Tanbo T. Birth defects in children conceived by ICSI compared with children conceived by other IVF-methods; a meta-analysis. Int J Epidemiol. 2004;34(3):696-701.*
- *Lieng M, Istre O, Sandvik L, Qvigstad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: Cross-sectional study. Journal of Minimally Invasive Gynecology. 2009;16(4):465-471.*
- *Lim KJH, Odukoya OA, Li TC, Cooke ID. Cytokines and immuno-endocrine factors in recurrent miscarriage. Hum Reprod Update. 1996;2(6):469-481.*
- *Lindqvist PG, Svensson PJ, Maršál K, Grennert L, Luterkort M, Dahlbäck B. Activated protein C resistance (FV: Q506) and pregnancy. Thromb Haemost. 1999;81(04):532-537.*
- *Llácer J, Bernabéu A, Bernabéu R. "Estudios genéticos en la disfunción reproductiva. diagnóstico genético preimplantatorio. consejo preconcepcional. Guía de Práctica Clínica de la SEF-SEGO.*
- *Lo W, Rai R, Hameed A, Brailsford SR, Al-Ghamdi AA, Regan L. The effect of body mass index on the outcome of pregnancy in women with recurrent miscarriage. Journal of family & community medicine. 2012;19(3):167.*
- *Lv SS, Wang JY, Wang XQ, Wang Y, Xu Y. Serum vitamin D status and in vitro fertilization outcomes: A systematic review and meta-analysis. Arch Gynecol Obstet. 2016;293(6):1339-1345.*
- *MacLennan M, Crichton JH, Playfoot CJ, Adams IR. Oocyte development, meiosis and aneuploidy. 2015;45:68-76.*
- *Mahadevan U, Sandborn WJ, Li D, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: A large community-based study from northern california. Gastroenterology. 2007;133(4):1106-1112.*
- *Malekasgar AM. ABO blood group prevalence in spontaneously repeated abortion. Turk J Haematol. 2004;2004(21):181-187.*
- *Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Fertil Steril. 2010;94(4):1473-1477.*
- *Martinelli I, Taioli E, Cetin I, et al. Mutations in coagulation factors in women with unexplained late fetal loss. N Engl J Med. 2000;343(14):1015-1018.*
- *Masoudian P, Nasr A, de Nanassy J, Fung-Kee-Fung K, Bainbridge SA, El Demellawy D. Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: A systematic review and metaanalysis. Obstet Gynecol. 2016;214(3):328-339.*
- *McLachlan SM, Rapoport B. Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: Potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. Thyroid. 2013;23(1):14-24.*
- *Meinardi JR, Middeldorp S, de Kam PJ, et al. Increased risk for fetal loss in carriers of the factor V leiden mutation. Ann Intern Med. 1999;130(9):736-739.*
- *Menasha J, Levy B, Hirschhorn K, Kardon NB. Incidence and spectrum of chromosome abnormalities in spontaneous abortions: New insights from a 12-year study. Genetics in medicine. 2005;7(4):251-263.*
- *Metwally M, Preece R, Thomas J, Ledger W, Li TC. A proteomic analysis of the endometrium in obese and overweight women with recurrent miscarriage: Preliminary evidence for an endometrial defect. Reproductive Biology and Endocrinology. 2014;12(1):75.*
- *Metwally M, Saravelos SH, Ledger WL, Li TC. Body mass index and risk of miscarriage in women with recurrent miscarriage. Fertil Steril. 2010;94(1):290-295.*
- *Metwally M, Tuckerman EM, Laird SM, Ledger WL, Li TC. Impact of high body mass index on endometrial morphology and function in the peri-implantation period in women with recurrent miscarriage. Reproductive biomedicine online. 2007;14(3):328-334.*
- *Middeldorp S. Thrombophilia and pregnancy complications: Cause or association? Journal of Thrombosis and Haemostasis. 2007;5:276-282.*

- *Miller E, Hare JW, Cloherty JP, et al. Elevated maternal hemoglobin A1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. Obstet Gynecol Surv. 1982;37(2):111-113.*
- *Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. N Engl J Med. 1988;319(25):1617-1623.*
- *Mir P, Al-Asmar N, Rodrigo L, Simon C, Rubio C. Debate: Should preimplantation genetic screening be performed in recurrent pregnancy loss? yes. Recurrent Pregnancy Loss: Causes, Controversies, and Treatment. 2014:55.*
- *Mir P, Al-Asmar N, Rodrigo L, Simon C, Rubio C. Debate: Should preimplantation genetic screening be performed in recurrent pregnancy loss? yes. Recurrent Pregnancy Loss: Causes, Controversies, and Treatment. 2014:55.*
- *Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis. 2006;4(2):295-306.*
- *Mizwicki MT, Norman AW. The vitamin D sterol–vitamin D receptor ensemble model offers unique insights into both genomic and rapid-response signaling. Sci.Signal. 2009;2(75):re4.*
- *Modi DN, Sane S, Bhartiya D. Accelerated germ cell apoptosis in sex chromosome aneuploid fetal human gonads. Mol Hum Reprod. 2003;9(4):219-225.*
- *Moffett A, Hiby SE, Sharkey AM. The role of the maternal immune system in the regulation of human birthweight. Philosophical Transactions of the Royal Society B: Biological Sciences. 2015;370(1663):20140071.*
- *Moffett A, Loke C. Immunology of placentation in eutherian mammals. Nature Reviews Immunology. 2006;6(8):584.*
- *Moffett A, Shreeve N. First do no harm: Uterine natural killer (NK) cells in assisted reproduction. Human reproduction. 2015;30(7):1519-1525.*
- *Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: Randomised double blind clinical trial. BMJ. 2006;332(7556):1485.*
- *Mollo A, Stile A, Alviggi C, et al. Endometrial polyps in infertile patients: Do high concentrations of interferon-gamma play a role? Fertil Steril. 2011;96(5):1209-1212.*
- *Munn S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. Fertil Steril. 1995;64(2):382-391.*
- *Munn S, Sandalinas M, Magli C, Gianaroli L, Cohen J, Warburton D. Increased rate of aneuploid embryos in young women with previous aneuploid conceptions. Prenat Diagn. 2004;24(8):638-643.*
- *Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. Fertil Steril. 2015;103(5):1215-1220.*
- *Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Human Reproduction. 2016;31(8):1668-1674.*
- *Musters AM, Repping S, Korevaar JC, et al. Pregnancy outcome after preimplantation genetic screening or natural conception in couples with unexplained recurrent miscarriage: A systematic review of the best available evidence. Fertil Steril. 2011;95(6):2157.e3.*
- *Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in finland. N Engl J Med. 2003;348(25):2517-2524.*
- *Nakimuli A, Chazara O, Farrell L, et al. Killer cell immunoglobulin-like receptor (KIR) genes and their HLA-C ligands in a ugandan population. Immunogenetics. 2013;65(11):765-775.*
- *Nakimuli A, Chazara O, Hiby SE, et al. A KIR B centromeric region present in africans but not europeans protects pregnant women from pre-eclampsia. Proceedings of the National Academy of Sciences. 2015;112(3):845-850.*
- *Nambiar V, Jagtap VS, Sarathi V, et al. Prevalence and impact of thyroid disorders on maternal outcome in asian-indian pregnant women. J Thyroid Res. 2011;2011:429097.*
- *Nardo LG, Rai R, Backos M, El-Gaddal S, Regan L. High serum luteinizing hormone and testosterone concentrations do not predict pregnancy outcome in women with recurrent miscarriage. Fertil Steril. 2002;77(2):348-352.*
- *Nasseri A, Mukherjee T, Grifo JA, Noyes N, Krey L, Copperman AB. Elevated day 3 serum follicle stimulating hormone and/or estradiol may predict fetal aneuploidy. Fertil Steril. 1999;71(4):715-718.*
- *Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. The Journal of Clinical Endocrinology & Metabolism. 2010;95(4):1699-1707.*
- *Nelson SM, Telfer EE, Anderson RA. The ageing ovary and uterus: New biological insights. Hum Reprod Update. 2012;19(1):67-83.*
- *Nicolaidis P, Petersen MB. Origin and mechanisms of non-disjunction in human autosomal trisomies. Human Reproduction. 1998;13(2):313-319.*

- *Nigro G, Mazzocco M, Mattia E, Di Renzo GC, Carta G, Anceschi MM. Role of the infections in recurrent spontaneous abortion. The Journal of Maternal-fetal & Neonatal Medicine. 2011;24(8):983-989.*
- *Nikitina TV, Sazhenova EA, Tolmacheva EN, et al. Comparative cytogenetic analysis of spontaneous abortions in recurrent and sporadic pregnancy losses. Biomedicine Hub. 2016;1(1):446099.*
- *No GG. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. April 2011. 2011.*
- *No GG. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. April 2011. 2011.*
- *No GG. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. April 2011. 2011.*
- *Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertil Steril. 2000;73(2):300-304.*
- *Ogasawara M, Kajiura S, Katano K, Aoyama T, Aoki K. Are serum progesterone levels predictive of recurrent miscarriage in future pregnancies? Fertil Steril. 1997;68(5):806-809.*
- *Olsen A, Duale N, Bjørås M, et al. Limited repair of 8-hydroxy-7, 8-dihydroguanine residues in human testicular cells. Nucleic Acids Res. 2003;31(4):1351-1363.*
- *Olsen NJ, Kovacs WJ. Gonadal steroids and immunity. Endocr Rev. 1996;17(4):369-384.*
- *Ota K, Dambaeva S, Han A, Beaman K, Gilman-Sachs A, Kwak-Kim J. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Human reproduction. 2013;29(2):208-219.*
- *Ozkan S, Jindal S, Greenseid K, et al. Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertil Steril. 2010;94(4):1314-1319.*
- *Page JM, Silver RM. Genetic causes of recurrent pregnancy loss. Clin Obstet Gynecol. 2016;59(3):498-508.*
- *Palermo GD, Colombero LT, Hariprashad JJ, Schlegel PN, Rosenwaks Z. Chromosome analysis of epididymal and testicular sperm in azoospermic patients undergoing ICSI. Human Reproduction. 2002;17(3):570-575.*
- *Palomba S, Falbo A, Orio Jr F, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2009;92(5):1646-1658.*
- *Pasquino AM, Passeri F, Pucarelli I, Segni M, Municchi G. Spontaneous pubertal development in turner's syndrome. The Journal of Clinical Endocrinology & Metabolism. 1997;82(6):1810-1813.*
- *Passamonti F, Randi ML, Rumi E, et al. Increased risk of pregnancy complications in patients with essential thrombocythemia carrying the JAK2 (617V> F) mutation. Blood. 2007;110(2):485-489.*
- *Pauer H, Burfeind P, Köstering H, Emons G, Hinney B. Factor XII deficiency is strongly associated with primary recurrent abortions. Fertil Steril. 2003;80(3):590-594.*
- *Pecks U, Maass N, Neulen J. Oocyte donation: A risk factor for pregnancy-induced hypertension: A meta-analysis and case series. Deutsches Ärzteblatt International. 2011;108(3):23.*
- *Pellicano M, Guida M, Zullo F, Lavitola G, Cirillo D, Nappi C. Carbon dioxide versus normal saline as a uterine distension medium for diagnostic vaginoscopic hysteroscopy in infertile patients: A prospective, randomized, multicenter study. Fertil Steril. 2003;79(2):418-421.*
- *Pereza N, Ostojić S, Kapović M, Peterlin B. Systematic review and meta-analysis of genetic association studies in idiopathic recurrent spontaneous abortion. Fertil Steril. 2017;107(1):159. e2.*
- *Perrin A, Basinko A, Douet-Guilbert N, et al. Aneuploidy and DNA fragmentation in sperm of carriers of a constitutional chromosomal abnormality. Cytogenetic and genome research. 2011;133(2-4):100-106.*
- *Piccinni M, Scaletti C, Maggi E, Romagnani S. Role of hormone-controlled Th1-and Th2-type cytokines in successful pregnancy. J Neuroimmunol. 2000;109(1):30-33.*
- *Pinder M, Lummis K, Selinger CP. Managing inflammatory bowel disease in pregnancy: Current perspectives. Clinical and experimental gastroenterology. 2016;9:325.*
- *Pluchino N, Drakopoulos P, Wenger JM, Petignat P, Streuli I, Genazzani AR. Hormonal causes of recurrent pregnancy loss (RPL). Hormones (Athens). 2014;13(3):314-322.*
- *Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88(10):3698-3703.*
- *Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Hum Reprod Update. 2003;9(2):149-161.*
- *Porter TF, Scott JR. Evidence-based care of recurrent miscarriage. Best practice & research Clinical obstetrics & gynaecology. 2005;19(1):85-101.*

- *Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: A guideline. Fertil Steril. 2015;104(3):545-553.*
- *Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: A committee opinion. Fertil Steril. 2012;98(5):1103-1111.*
- *Practice Committee of the American Society for Reproductive Medicine. The clinical utility of sperm DNA integrity testing: A guideline. Fertil Steril. 2013;99(3):673-677.*
- *Pratt DE, Kaberlein G, Dudkiewicz A, Karande V, Gleicher N. The association of antithyroid antibodies in euthyroid nonpregnant women with recurrent first trimester abortions in the next pregnancy. Fertil Steril. 1993;60(6):1001-1005.*
- *Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia. The Lancet. 1996;348(9032):913-916.*
- *Propst AM, Hill III JA. Anatomic factors associated with recurrent pregnancy loss. . 2000;18(04):341-350.*
- *Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. Fertil Steril. 2011;95(8):2690-2692.*
- *Rai R, Backos M, Elgaddal S, Shlebak A, Regan L. Factor V leiden and recurrent miscarriage—prospective outcome of untreated pregnancies. Human reproduction. 2002;17(2):442-445.*
- *Rai R, Backos M, Rushworth F, Regan L. Polycystic ovaries and recurrent miscarriage—a reappraisal. Human Reproduction. 2000;15(3):612-615.*
- *Rai R, Regan L. Recurrent miscarriage. The Lancet. 2006;368(9535):601-611.*
- *Rao V, Lakshmi A, Sadhnani M. Prevalence of hypothyroidism in recurrent pregnancy loss in first trimester. Indian J Med Sci. 2008;62(9):359.*
- *Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: A meta-analysis. QJM. 2001;94(8):435-444.*
- *Revel A. Defective endometrial receptivity. Fertil Steril. 2012;97(5):1028-1032.*
- *Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: A meta-analysis. The Lancet. 2003;361(9361):901-908.*
- *Richlin SS, Ramachandran S, Shanti A, Murphy AA, Parthasarathy S. Glycodelin levels in uterine flushings and in plasma of patients with leiomyomas and polyps: Implications for implantation. Human Reproduction. 2002;17(10):2742-2747.*
- *Ridker PM, Miletich JP, Buring JE, et al. Factor V leiden mutation as a risk factor for recurrent pregnancy loss. Ann Intern Med. 1998;128(12_Part_1):1000-1003.*
- *Rikken JF, Kowalik CR, Emanuel MH, et al. Septum resection for women of reproductive age with a septate uterus. The Cochrane Library. 2017.*
- *Rius M, Obradors A, Daina G, et al. Detection of unbalanced chromosome segregations in preimplantation genetic diagnosis of translocations by short comparative genomic hibridization. Fertil Steril. 2011;96(1):134-142.*
- *Robberecht C, Pexsters A, Deprest J, Fryns J, D'hooghe T, Vermeesch JR. Cytogenetic and morphological analysis of early products of conception following hystero-embryoscopy from couples with recurrent pregnancy loss. Prenat Diagn. 2012;32(10):933-942.*
- *Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: A systematic review. Br J Haematol. 2006;132(2):171-196.*
- *Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: A systematic review. Br J Haematol. 2006;132(2):171-196.*
- *Robinson L, Gallos ID, Conner SJ, et al. The effect of sperm DNA fragmentation on miscarriage rates: A systematic review and meta-analysis. Human Reproduction. 2012;27(10):2908-2917.*
- *Rodrguez E, Gil-Villa AM, Aguirre-Acevedo DC, Cardona-Maya W. Evaluacin de parmetros seminales no convencionales en individuos cuyas parejas presentan muerte embrionaria temprana recurrente: En busca de un valor de referencia. Biomedica. 2011;31(1):100-107.*
- *Rodrigo L, Mateu E, Mercader A, et al. New tools for embryo selection: Comprehensive chromosome screening by array comparative genomic hybridization. BioMed research international. 2014;2014.*
- *Rosendaal FR. Venous thrombosis: A multicausal disease. The Lancet. 1999;353(9159):1167-1173.*
- *Rubio C, Gil-Salom M, Simon C, et al. Incidence of sperm chromosomal abnormalities in a risk population: Relationship with sperm quality and ICSI outcome. Human Reproduction. 2001;16(10):2084-2092.*
- *Rubio C, Simon C, Vidal F, et al. Chromosomal abnormalities and embryo development in recurrent miscarriage couples. Human Reproduction. 2003;18(1):182-188.*
- *Rubio C, Simon C, Vidal F, et al. Chromosomal abnormalities and embryo development in recurrent miscarriage couples. Human Reproduction. 2003;18(1):182-188.*
- *Rubio C, Buenda P, Rodrigo L, et al. Prognostic factors for preimplantation genetic screening in repeated pregnancy loss. Reproductive biomedicine online. 2009;18(5):687-693.*
- *Rubio C, Rodrigo L, Mir P, et al. Use of array comparative genomic hybridization (array-CGH) for embryo assessment: Clinical results. Fertil Steril. 2013;99(4):1044-1048.*

- *Rubio C, Simn C, Blanco J, et al. Implications of sperm chromosome abnormalities in recurrent miscarriage. J Assist Reprod Genet. 1999;16(5):253-258.*
- *Ruixue W, Hongli Z, Zhihong Z, Rulin D, Dongfeng G, Ruizhi L. The impact of semen quality, occupational exposure to environmental factors and lifestyle on recurrent pregnancy loss. J Assist Reprod Genet. 2013;30(11):1513-1518.*
- *Rull K, Nagirnaja L, Laan M. Genetics of recurrent miscarriage: Challenges, current knowledge, future directions. Frontiers in genetics. 2012;3:34.*
- *Saccone G, Berghella V, Maruotti GM. PREGNANTS (PREGNancy in women with ANTiphospholipid syndrome) working group. Obstet Gynecol. 2017;216(525):1.*
- *Sacks G. Enough! stop the arguments and get on with the science of natural killer cell testing. Human Reproduction. 2015;30(7):1526-1531.*
- *Sanson BJ, Friedrich PW, Simioni P, et al. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. Thromb Haemost. 1996;75(03):387-388.*
- *Saravelos SH, Cocksedge KA, Li T. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: A critical appraisal. Hum Reprod Update. 2008;14(5):415-429.*
- *Saravelos SH, Li T. Unexplained recurrent miscarriage: How can we explain it? Human reproduction. 2012;27(7):1882-1886.*
- *Saravelos SH, Yan J, Rehmani H, Li T. The prevalence and impact of fibroids and their treatment on the outcome of pregnancy in women with recurrent miscarriage. Human reproduction. 2011;26(12):3274-3279.*
- *Sata F, Yamada H, Kishi R, Minakami H. Maternal folate, alcohol and energy metabolism-related gene polymorphisms and the risk of recurrent pregnancy loss. Journal of developmental origins of health and disease. 2012;3(5):327-332.*
- *Sata F, Yamada H, Suzuki K, et al. Caffeine intake, CYP1A2 polymorphism and the risk of recurrent pregnancy loss. Mol Hum Reprod. 2005;11(5):357-360.*
- *Savulescu J. Procreative beneficence: Why we should select the best children. Bioethics. 2001;15(5-6):413-426.*
- *Savulescu J, Pugh J, Douglas T, Gyngell C. The moral imperative to continue gene editing research on human embryos. Protein & cell. 2015;6(7):476-479.*
- *Scott RT, Snyder RR, Bagnall JW, Reed KD, Adair CF, Hensley SD. Evaluation of the impact of intraobserver variability on endometrial dating and the diagnosis of luteal phase defects. Fertil Steril. 1993;60(4):652-657.*
- *Seoane RJ. [From genetic privacy to the right to genetic data protection. basic protection of genetic data in spanish law (regarding SSTC290/2000 and 292/2000, of november 30)(II)]. Revista de derecho y genoma humano= Law and the human genome review. 2001(17):135-175.*
- *Shahine LK, Lathi RB. Embryo selection with preimplantation chromosomal screening in patients with recurrent pregnancy loss. . 2014;32(02):93.*
- *Shamsi MB, Imam SN, Dada R. Sperm DNA integrity assays: Diagnostic and prognostic challenges and implications in management of infertility. J Assist Reprod Genet. 2011;28(11):1073-1085.*
- *Sharshiner R, Romero ST, Bardsley TR, Branch DW, Silver RM. Celiac disease serum markers and recurrent pregnancy loss. J Reprod Immunol. 2013;100(2):104-108.*
- *Sierra S, Stephenson M. Genetics of recurrent pregnancy loss. . 2006;24(01):17.*
- *Silver RM, Branch D. Sporadic and recurrent pregnancy loss. Handbook of Clinical Obstetrics: The Fetus & Mother, Third Edition. 2008:41-46.*
- *Silver RM, Zhao Y, Spong CY, et al. Prothrombin gene G20210A mutation and obstetric complications. Obstet Gynecol. 2010;115(1):14.*
- *Simon C, Rubio C, Vidal F, et al. Increased chromosome abnormalities in human preimplantation embryos after in-vitro fertilization in patients with recurrent miscarriage. Reproduction, fertility and development. 1998;10(1):87-92.*
- *Simon L, Castillo J, Oliva R, Lewis SE. Relationships between human sperm protamines, DNA damage and assisted reproduction outcomes. Reproductive biomedicine online. 2011;23(6):724-734.*
- *Snchez-Castro M, Jimnez-Macedo AR, Sandalinas M, Blanco J. Prognostic value of sperm fluorescence in situ hybridization analysis over PGD. Human reproduction. 2009;24(6):1516-1521.*
- *Somers EC, Marder W. Infertility–Prevention and management. Rheumatic Disease Clinics. 2017;43(2):275-285.*
- *Soria JM, Almasy L, Souto JC, et al. A quantitative-trait locus in the human factor XII gene influences both plasma factor XII levels and susceptibility to thrombotic disease. The American Journal of Human Genetics. 2002;70(3):567-574.*
- *Soria JM, Morange P, Vila J, et al. Multilocus genetic risk scores for venous thromboembolism risk assessment. Journal of the American Heart Association. 2014;3(5):e001060.*
- *Souto JC, Almasy L, Borrell M, et al. Genetic susceptibility to thrombosis and its relationship to physiological risk factors: The GAIT study. The American Journal of Human Genetics. 2000;67(6):1452-1459.*
- *Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins; 2005.*

- *Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the american thyroid association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21(10):1081-1125.*
- *Stefanidou EM, Caramellino L, Patriarca A, Menato G. Maternal caffeine consumption and sine causa recurrent miscarriage. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2011;158(2):220-224.*
- *Stephenson MD, Awartani KA, Robinson WP. Cytogenetic analysis of miscarriages from couples with recurrent miscarriage: A case–control study. Human Reproduction. 2002;17(2):446-451.*
- *Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Human Reproduction. 2006;21(4):1076-1082.*
- *Stephenson M, Kutteh W. Evaluation and management of recurrent early pregnancy loss. Clin Obstet Gynecol. 2007;50(1):132-145.*
- *Strassmann EO. Fertility and unification of double uterus. Fertil Steril. 1966;17(2):165-176.*
- *Sugiura-Ogasawara M, Lin BL, Aoki K, et al. Does surgery improve live birth rates in patients with recurrent miscarriage caused by uterine anomalies? Journal of Obstetrics and Gynaecology. 2015;35(2):155-158.*
- *Sugiura-Ogasawara M. Recurrent pregnancy loss and obesity. Best Practice & Research Clinical Obstetrics & Gynaecology. 2015;29(4):489-497.*
- *Sugiura-Ogasawara M, Ozaki Y, Katano K, Suzumori N, Kitaori T, Mizutani E. Abnormal embryonic karyotype is the most frequent cause of recurrent miscarriage. Human reproduction. 2012;27(8):2297-2303.*
- *Sullivan AE, Silver RM, LaCoursiere DY, Porter TF, Branch DW. Recurrent fetal aneuploidy and recurrent miscarriage. Obstetrics & Gynecology. 2004;104(4):784-788.*
- *Suzumori N, Sugiura-Ogasawara M. Genetic factors as a cause of miscarriage. Curr Med Chem. 2010;17(29):3431-3437.*
- *Tal J, Schliamser LM, Leibovitz Z, Ohel G, Attias D. A possible role for activated protein C resistance in patients with first and second trimester pregnancy failure. Human Reproduction. 1999;14(6):1624-1627.*
- *Tata LJ, Card TR, Logan R, Hubbard RB, Smith C, West J. Fertility and pregnancy-related events in women with celiac disease: A population-based cohort study. Gastroenterology. 2005;128(4):849-855.*
- *Taylor E, Gomel V. The uterus and fertility. Fertil Steril. 2008;89(1):1-16.*
- *Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: Meta-analysis of evidence. BMJ. 2011;342:d2616.*
- *Theisen A. Microarray-based comparative genomic hybridization (aCGH). Nature Education. 2008;1(1):45.*
- *Tirado I, Soria JM, Mateo J, et al. Association after linkage analysis indicates that homozygosity for the 46Cβ T polymorphism in the F12 gene is a genetic risk factor for venous thrombosis. Thromb Haemost. 2004;92(05):899-904.*
- *Toulis KA, Goulis DG, Venetis CA, et al. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: A meta-analysis. Eur J Endocrinol. 2010;162(4):643-652.*
- *Tso LO, Costello MF, Andriolo RB, Freitas V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2009(2).*
- *Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2014(11).*
- *Tursi A, Giorgetti G, Brandimarte G, Elisei W. Effect of gluten-free diet on pregnancy outcome in celiac disease patients with recurrent miscarriages. Dig Dis Sci. 2008;53(11):2925-2928.*
- *Uhrberg M, Valiante NM, Shum BP, et al. Human diversity in killer cell inhibitory receptor genes. Immunity. 1997;7(6):753-763.*
- *Unuane D, Velkeniers B, Deridder S, Bravenboer B, Tournaye H, De Brucker M. Impact of thyroid autoimmunity on cumulative delivery rates in in vitro fertilization/intracytoplasmic sperm injection patients. Fertil Steril. 2016;106(1):144-150.*
- *Vaiman D. Genetic regulation of recurrent spontaneous abortion in humans. Biomedical journal. 2015;38(1):11-24. http://www.ncbi.nlm.nih.gov/pubmed/25179715. doi: 10.4103/2319-4170.133777.*
- *van de Vijver A, Drakopoulos P, Van Landuyt L, et al. Vitamin D deficiency and pregnancy rates following frozen–thawed embryo transfer: A prospective cohort study. Human Reproduction. 2016;31(8):1749-1754.*
- *van den Berg, Merel MJ, van Maarle MC, van Wely M, Goddijn M. Genetics of early miscarriage. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2012;1822(12):1951-1959.*
- *Van den Berg M, Vissenberg R, Goddijn M. Recurrent miscarriage clinics. Obstet Gynecol Clin North Am. 2014;41(1):145-155.*
- *Varasteh NN, Neuwirth RS, Levin B, Keltz MD. Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. Obstetrics & Gynecology. 1999;94(2):168-171.*
- *Vasilevska M, Ivanovska E, Kubelka Sabit K, Sukarova-Angelovska E, Dimeska G. The incidence and type of chromosomal translocations from prenatal diagnosis of 3800 patients in the republic of macedonia. Balkan Journal of Medical Genetics. 2013;16(2):23-28.*
- *Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: A systematic review and meta-analysis. Human reproduction. 2014;29(5):964-977.*

- *Vidal F, Gimenez C, Rubio C, et al. FISH preimplantation diagnosis of chromosome aneuploidy in recurrent pregnancy wastage. J Assist Reprod Genet. 1998;15(5):310-313.*
- *Voskuhl RR, Pitchekian-Halabi H, Mackenzie-Graham A, McFarland HF, Raine CS. Gender differences in autoimmune demyelination in the mouse: Implications for multiple sclerosis. Ann Neurol. 1996;39(6):724-733.*
- *Vossen CY, Preston FE, Conard J, et al. Hereditary thrombophilia and fetal loss: A prospective follow-up study. Journal of Thrombosis and Haemostasis. 2004;2(4):592-596.*
- *Wallenius M, Salvesen KÅ, Daltveit AK, Skomsvoll JF. Miscarriage and stillbirth in women with rheumatoid arthritis. J Rheumatol. 2015:jrheum. 141553.*
- *Wang ET, Calderon-Margalit R, Cedars MI, et al. Polycystic ovary syndrome and risk for long-term diabetes and dyslipidemia. Obstet Gynecol. 2011;117(1):6.*
- *Wapner RJ, Lewis D. Genetics and metabolic causes of stillbirth. . 2002;26(1):70-74.*
- *Warburton D, Kline J, Stein Z, Hutzler M, Chin A, Hassold T. Does the karyotype of a spontaneous abortion predict the karyotype of a subsequent abortion? evidence from 273 women with two karyotyped spontaneous abortions. Am J Hum Genet. 1987;41(3):465.*
- *Warburton D, Kline J, Stein Z, Hutzler M, Chin A, Hassold T. Does the karyotype of a spontaneous abortion predict the karyotype of a subsequent abortion? evidence from 273 women with two karyotyped spontaneous abortions. Am J Hum Genet. 1987;41(3):465.*
- *Warren JE, Silver RM. Genetics of pregnancy loss. Clin Obstet Gynecol. 2008;51(1):84-95.*
- *Wilcox AJ, Weinberg CR, O'connor JF, et al. Incidence of early loss of pregnancy. N Engl J Med. 1988;319(4):189-194.*
- *Williamson D, Brown K, Luddington R, Baglin C, Baglin T. Factor V cambridge: A new mutation (Arg306βthr) associated with resistance to activated protein C. Blood. 1998;91(4):1140-1144.*
- *Wold ASD, Pham N, Arici A. Anatomic factors in recurrent pregnancy loss. . 2006;24(01):25.*
- *Wolf GC, Mao J, Izquierdo L, Joffe G. Paternal pericentric inversion of chromosome 4 as a cause of recurrent pregnancy loss. J Med Genet. 1994;31(2):153-155.*
- *Wolf GC, Horger EO. Indications for examination of spontaneous abortion specimens: A reassessment. Obstet Gynecol. 1995;173(5):1364-1368.*
- *Yan X, Wang L, Yan C, et al. Decreased expression of the vitamin D receptor in women with recurrent pregnancy loss. Arch Biochem Biophys. 2016;606:128-133.*
- *Yao R, Goetzinger KR. Genetic carrier screening in the twenty-first century. Clin Lab Med. 2016;36(2):277-288.*
- *Zhang B, Wei Y, Niu J, Li Y, Miao Z, Wang Z. Risk factors for unexplained recurrent spontaneous abortion in a population from southern china. International Journal of Gynecology & Obstetrics. 2010;108(2):135-138.*
- *Zorrilla M, Yatsenko AN. The genetics of infertility: Current status of the field. Current genetic medicine reports. 2013;1(4):247-260.*

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