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Review Article

An Update on Etiology and Management of Recurrent Pregnancy Loss

NAHREEN AKHTAR[1], MEEM SHAHRIN[2], SYEDA SAYEEDA[1], TABASSUM PARVEEN[3]

Abstract:

Recurrent Pregnancy Loss (RPL) is a complex health challenge with no universally accepted definition. Incidence of recurrent miscarriage is reported to range from 1% to 3%. The exact etiology of recurrent pregnancy loss remains questionable; thus, it is considered a polyetiological and multifactorial condition with many modifiable and non-modifiable factors involved. Known risk factors for RPL are maternal age, previous pregnancy losses, parental chromosomal abnormalities, uterine morphological pathologies, endocrine disturbances, antiphospholipid syndrome (APS), inherited thrombophilia and infectious agents. However, even after thoroughly evaluating recurrent pregnancy loss etiology and risk factors, up to 75% of cases remain unexplained. This review aimed to summarize accumulated knowledge on the etiology, risk factors and management approach to recurrent pregnancy loss.

Key words: *Maternal age, Eudorine disorder,Thrombophilia, Autoimmune disorder*

Introduction:

The Royal College of Obstetricians and Gynaecologists defines recurrent miscarriage as three or more first trimester miscarriages.[1] The American Society for Reproductive Medicine Practice Committee defines RPL as two or more miscarriages; that is pregnancies with the same partner and documented by ultrasonography or histopathological examination.[2]The most recent RPL guideline from European Society of Human Reproduction and Embryology (ESHRE) set the definition after a significant debate. It states that RPL could be considered after the loss of two or more pregnancies.[3]

Recurrent pregnancy loss (RPL) occurs in 1–3% of all couples trying to conceive.[4]

According to a worldwide estimation, 23 million cases occur annually.[5] In low-and middle-income countries, no conclusive research explains the prevalence of women with a history of recurrent pregnancy loss (RPL).[6]

The problem is underestimated as a simple physical health issue, which in most cases does not lead to serious health consequences. However, the psychological impact of the event is far more serious than the clinical presentation and subsequent physical harm.[5, 7]

RPL is one of the challenging scenarios in reproductive medicine, and it is frustrating for the patients, their families, and treating physicians.

Methods:

This non-systematic narrative review article searched articles over last 10 years by using the search term 'Etiologies and Management of Recurrent Pregnancy Loss' in PubMed and Google Scholar with the aim to provide a reasonably updated evidence based approach to etiologies and management of recurrent pregnancy loss. Only the articles on or after the year 2006 has been cited. One author prepared the initial draft, and others contributed intellectually to make it a final one after several modifications. No statistical analysis was conducted on the data included in the original articles, and detailed numerical presentations were avoided. All types of articles were included. Before submission, the draft was thoroughly discussed by the final round of corrections.

1. Professor, Department of Fetomaternal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka.
2. Dr. Meem Shahrin, Junior Consultant, OSD (DGHS), Department of Fetomaternal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka.
3. Professor & Chairman, Department of Fetomaternal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Pathophysiology

RPL is a multifactorial condition that may be due to genetic, anatomic, endocrine, antiphospholipid antibody syndrome, immunologic, and environmental factors.

FOXD1 mutations play a central role in RPL. FOXD1 is defined as a major molecule involved in embryo implantation in mice and humans by regulating endometrial and placental genes. FOXD1 mutations in human species have been functionally linked to RPL's origin. [8]

Etiologies

It is considered a polyetiological and multifactorial condition with many modifiable and non-modifiable factors involved. Even after thoroughly evaluating recurrent pregnancy loss etiology and risk factors, up to 75% of cases remain unexplained.[9]

Known risk factors for RPL are maternal age, previous pregnancy losses, parental chromosomal abnormalities, uterine morphological pathologies, endocrine disturbances, antiphospholipid syndrome (APS), inherited thrombophilia and infectious agents.[4,9]

Maternal Age

Women's age at conception is reported to serve as an independent risk factor for miscarriage. [9v]The risk was moderately increased (15.8%) for women under the age of 20, with the absolute lowest risk (9.5%) at age 27, and then rising nearly linearly after the age of 30 to reach 54% at ages 45 and over.[10]

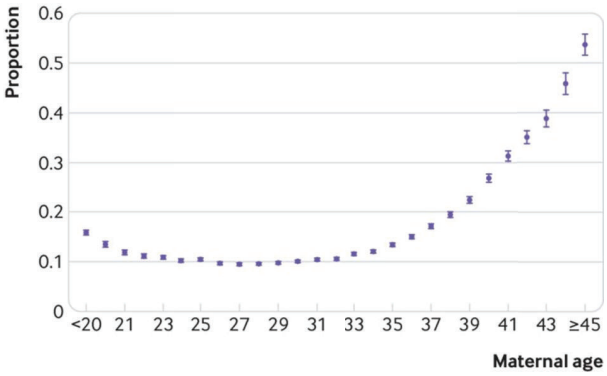

Figure 1: *Risk of miscarriage according to maternal age. The bars for each point reflect the 95% confidence intervals.*[9]

According to the RCOG guideline data, the age-related risk of pregnancy loss is 13% in d"19 years; 11–12% in 20–29 years; 15% in 30–34 years; 25% in 35–39 years; 51% in 40–44 years; and 93% in e"45 years age groups. [9]

Previous Pregnancy Losses

Controlling for maternal age, the odds ratio for miscarriage increased from 1.5 after one miscarriage to 2.2 after two and 4.0 after three. Recurrence risk has been previously reported, although not with this precision or to this extent.[11]

There is evidence that certain other pregnancy outcomes cluster with the risk of miscarriage, suggesting that these outcomes might share underlying causes. Specifically, the risk of miscarriage was moderately increased among women who had experienced a stillbirth, preterm delivery, or gestational diabetes in their previous pregnancy.[10]

According to the updated 2022 ESHRE guideline, women's age, together with precise and complete pregnancy history, are important in predicting the live birth chances in the next pregnancy.[3] Therefore, the recent ESHRE recommendations suggest setting up a prognosis based on the woman's age, complete pregnancy history, including a number of previous pregnancy losses, live births, and their sequence. [3]

Parental chromosomal abnormalities

Well-known genetic causes of RPL are gross chromosomal defects and variations of allelic expression.[12] The frequency of karyotype abnormality affects approximately 2–8% of couples with RPL. [13]

Uterine morphological pathologies

The contribution of uterine structural anomalies to the etiology of RPL has been reported in several studies and found to be present in about 7–28% of women with RPL compared with 4–7% of women in the general population. [9]

The most common congenital uterine anomalies include septate uteri, arcuate, and bicorporal uteri. [13] Among patients with congenital uterine defects, women with a septate uteri have the highest incidence of recurrent miscarriage—44.3%, patients with bicornuate uteri—36%, and arcuate uteri—25.7%. [13]

Acquired uterine structural defects such as submucosal uterine leiomyomas, endometrial synechiae, and polyps interfere with the process of

implantation and embryo development, thus, may result in recurrent miscarriage.[13, 14] These conditions are associated with 6–15% of RPL. [14,15, 16]

Endocrine Disorders

It is estimated that approximately 8% to 12% of all cases of recurrent pregnancy loss (RPL) are caused by endocrine diseases.[17] Indeed, the local hormonal milieu is crucial in both embryo attachment and early pregnancy.

Endocrine abnormalities, including thyroid disorders, luteal phase defects, polycystic ovary syndrome, prolactin level abnormality and diabetes have to be evaluated in any case of RPL. Moreover, elevated androgen levels and some endocrinological aspects of endometriosis are also factors contributing to RPL. [18]

Thyroid disorders: Even though subclinical hypothyroidism does not increase the risk of RPL,[19] clinically recognizable hypothyroidism cases with moderate and significant elevated thyroid-stimulating hormone (TSH) is a well-known risk factor for miscarriage [7,20,21] and impaired fetal and newborn development. [21, 22]

Luteal Phase Deficiency: Since progesterone plays a major physiologic role in the process of successful implantation and pregnancy development, [19, 23] insufficient progesterone levels (i.e., luteal phase deficiency) are assumed to be associated with spontaneous pregnancy loss. [13, 20, 24]

Polycystic Ovarian Syndrome (PCOS) and 0besity: Polycystic ovarian syndrome (PCOS) is not considered a predictive factor for RPL.[25] However, obesity itself or related to PCOS increases the risk of recurrent miscarriage.[9]

Prolactin Level Abnormality: High prolactin in early follicular growth may inhibit progesterone secretion, which results in luteal phase defects. [26] On the other hand, one study revealed that lower basal serum prolactin concentration is associated with an increased risk of miscarriage in a subsequent pregnancy in women with unexplained recurrent miscarriage. [27]

Rate of successful pregnancy is higher in hyperprolactinemic women with Recurrent spontaneous abortion (RSA) who are treated with bromocriptine during randomized control trial. [28]

Diabetes Mellitus: The RCOG guideline suggests that well-controlled diabetes is not a risk factor for recurrent miscarriage, while poorly controlled diabetes with high levels of HbA1c is. [13,15,19]

Antiphospholipid Syndrome (APS)

APS is an autoimmune condition featured by antiphospholipid antibody formation and associated with thrombotic events and pregnancy complications, including RPL.[9] The prevalence of antiphospholipid antibodies is estimated at 15–20% among women with RPL,[13,19,29,30] while in low-risk women, this indicator is less than 2% [19] Moreover, in women with RPL associated with APS, the live birth rate was reported to be low (10%) if no pharmacological management was applied. [18] The APS causes an inflammatory response to antiphospholipid antibodies on vascular endothelium and chorionic/placental cells, which promotes thrombosis. [19]

Inherited Thrombophilia

Thrombophilia and the predisposition to improper coagulation can affect chorionic blood flow and cause vasculopathy leading to pregnancy loss. [31, 32, 33] The most prevalent types of thrombophilia associated with RPL are hereditary (factor V Leiden, genetic polymorphism of methylenetetrahydrofolate reductase (MTHFR) enzyme, prothrombin gene mutation, protein C deficiency, etc.). [19,33]

Infectious Agents

Certain infections, including *Listeria monocytogenes, Toxoplasma gondii*, rubella, herpes simplex virus (HSV), measles, cytomegalovirus, and coxsackieviruses, are known or suspected to play a role in sporadic spontaneous pregnancy loss. [33] However, the role of infectious agents in recurrent loss is less clear, with a proposed incidence of 0.5%[35] to 5%.[36]

The proposed mechanisms for infectious causes of pregnancy loss include: (1) direct infection of the uterus, fetus, or placenta, (2) placental insufficiency, (3) chronic endometritis or endocervicitis, (4) amnionitis, or (5) infected intrauterine device. Because most of these are isolated events, it appears that there is a limited role for infections as a causative factor in RPL.[34]

Other risk factors

Other risk factors for RPL include vitamin D deficiency, stress, alcohol, smoking, ethnicity, a history of previous miscarriage and preterm.

Unexplained RPL (URPL)

URPL is considered the diagnosis if a complete genetic, anatomic, endocrine, and immune evaluation was performed and returned as normal.[37]

Treatment / Management

The treatment of RPL should be directed towards the underlying treatable cause. Patients and their families should be informed about the risks, alternatives, and success rates of each available treatment option. Treatment success can be increased by providing emotional support for these anxious couples. There should be collaborative teamwork and clear communication between reproductive endocrinologists and obstetricians whenever possible.

Medical Conditions

Women with thyroid conditions, diabetes, obesity, and other medical problems should be treated as medically appropriate. Consultation with an endocrinologist is also a suitable option for the management of uncontrolled thyroid conditions and diabetes. Patients with elevated thyroid peroxidase antibodies are at high risk for RPL and should be managed appropriately.[38]

Chromosomal Anomalies

In couples with chromosomal abnormalities, the first step is a referral to genetic counseling. Couples should be educated on the potential likelihood of having fetal chromosomal abnormalities in future pregnancies. They may choose to proceed with prenatal genetic testing, such as preimplantation genetic diagnosis, chorionic villus sampling, or amniocentesis to identify genetic anomalies in the fetus and decide about further treatment options. [39]

Although embryos with unbalanced chromosomal arrangements can theoretically be screened out, PGT (preimplantation genetic testing) is not routinely advised since the likelihood of a pregnancy with an unbalanced karyotype surviving into the second trimester is low.[40]

Uterine Anomalies

There is evidence that hysteroscopic septal division reduces pregnancy loss rates, resulting in live births. However, owing to a lack of high-quality evidence of the efficacy and safety of surgical treatment, this should only be offered on an individual basis by experienced specialists. [41]

Immunological

A meta analysis of randomized controlled trials assessed effects of heparin and/or aspirin on live birth rate in women with recurrent pregnancy loss and antiphospholipid antibodies and concluded that heparin plus aspirin may increase live birth rate. [42]

However, in women with thrombophilias, this treatment may improve maternal outcomes but does not prevent RPL. Treatment strategies like aspirin and low molecular weight heparin (LMWH) are standard medications in RPL, although only a few placebo-controlled trials have proven their benefit with respect to live birth rate. There is emerging evidence that new treatment options, including drugs like TNF (tumor necrosis factor-alpha) inhibitors and granulocyte colony-stimulating factor (G-CSF), might be beneficial in some cases of RPL. However, more extensive clinical trials must be completed to further prove or disprove the benefits of these drugs in the treatment of patients with RPL.[43] Lipid emulsion infusions have been evaluated in only one RCT that tested whether a 250 mL infusion on the day of oocyte retrieval (with further infusions if there was a positive pregnancy test) could increase chemical pregnancy rates in patients with RPL with elevated peripheral blood NK cells (more than 12 percent) undergoing IVF. [44] The study concluded that Intralipid supplementation did not increase the frequency of chemical pregnancy. However, findings related to ongoing pregnancy and live birth should be investigated further. [44]

Unexplained RPL

Prednisolone and IVIG are being used in different countries as a mode of treatment for recurrent pregnancy loss. A recent meta-analysis for unexplained RPL found no RCTs involving prednisolone in treatment for RPL. Two recent meta-analyses of intravenous immunoglobulin (IVIG) use in patients with RPL found no evidence of improved live birth rates. [45]

Conclusion:

Recurrent miscarriage is a traumatic life event that affects women's physical and psychological health and social well-being. Grounded on the up-to-date researches, the following risk factors should be investigated in patients with RPL: chromosomal abnormalities, congenital and acquired uterine pathologies, endocrine disorders, thrombophilia, and autoimmune diseases.

References:

1. RCOG Guidelines Committee. Recurrent Miscarriage (Green-top Guideline No. 17).19 June 2023. Available from: https://

www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/recurrent-miscarriage-green-top-guideline-no-17, accessed on 2nd October, 2023.

2. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012 Nov;98(5):1103-11.
3. The ESHRE Guideline Group on RPL. Atik R.B., Christiansen O.B., Elson J., Kolte A.M., Lewis S., Middeldorp S., Mcheik S., Peramo B., Quenby S., et al. ESHRE guideline: Recurrent pregnancy loss: An update in 2022. *Hum. Reprod. Open.* 2022;2023:hoad002.
4. van Dijk MM, Kolte AM, Limpens J, Kirk E, Quenby S, van Wely M, Goddijn M. Recurrent pregnancy loss: diagnostic workup after two or three pregnancy losses? A systematic review of the literature and meta-analysis. Hum Reprod Update. 2020 Apr 15;26(3):356-367.
5. Quenby S., Gallos I.D., Dhillon-Smith R.K., Podesek M., Stephenson M.D., Fisher J., Brosens J.J., Brewin J., Ramhorst R., Lucas E.S., et al. Miscarriage matters: The epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet.* 2021;397:1658–1667.
6. Eleje GU, Ugwu EO, Igbodike EP, Malachy DE, Nwankwo EU, Ugboaja JO, Ikechebelu JI and Nwagha UI (2023) Prevalence and associated factors of recurrent pregnancy loss in Nigeria according to different national and international criteria (ASRM/ESHRE vs. WHO/RCOG). *Front. Reprod. Health* 5:1049711.
7. La X., Wang W., Zhang M., Liang L. Definition and Multiple Factors of Recurrent Spontaneous Abortion. *Adv. Exp. Med. Biol.* 2021;1300:231–257.
8. Barišiæ A, Pereza N, Hod•iæ A, Krpina MG, Ostojiæ S, Peterlin B. Genetic variation in the maternal vitamin D receptor FokI gene as a risk factor for recurrent pregnancy loss. J Matern Fetal Neonatal Med. 2021 Jul;34(14):2221-2226.
9. Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldygulova L, Amanzholkyzy A, Ryzhkova S, Nogay A, Khamidullina Z, Ilmaliyeva A, Almawi WY, Atageldiyeva K. Recurrent Pregnancy Loss Etiology, Risk Factors, Diagnosis, and Management. Fresh Look into a Full Box. J Clin Med. 2023 Jun 15;12(12):4074
10. Magnus M C, Wilcox A J, Morken N, Weinberg C R, HÃ¥berg S E. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study *BMJ* 2019; 364 :l869
11. Bhattacharya S, Townend J, Bhattacharya S. Recurrent miscarriage: Are three miscarriages one too many? Analysis of a Scottish population-based database of 151,021 pregnancies. Eur J ObstetGynecolReprod Biol. 2010 May;150(1): 24-7.
12. Grimstad F., Krieg S. Immunogenetic contributions to recurrent pregnancy loss. *J. Assist. Reprod. Genet.* 2016;33:833–847.
13. Khalife D., Ghazeeri G., Kutteh W. Review of current guidelines for recurrent pregnancy loss: New strategies for optimal evaluation of women who may be superfertile. *Semin. Perinatol.* 2019;43:105–115.
14. Carbonnel M., Pirtea P., de Ziegler D., Ayoubi J.M. Uterine factors in recurrent pregnancy losses. *Fertil. Steril.* 2021;115:538–545.
15. Li Y.H., Marren A. Recurrent pregnancy loss: A summary of international evidence-based guidelines and practice. *Aust. J. Gen. Pract.* 2018;47:432–436.
16. Ono S., Yonezawa M., Watanabe K., Abe T., Mine K., Kuwabara Y., Akira S., Takeshita T. Retrospective cohort study of the risk factors for secondary infertility following hysteroscopic metroplasty of the uterine septum in women with recurrent pregnancy loss. *Reprod. Med. Biol.* 2017;17:77–81.
17. 16 Malik Priyanka, Garg Yogesh, Bedi Gurdeep Kaur, Vij Chittranjan. Endocrine Dysfunction in Recurrent Pregnancy Loss. International Journal of Contemporary Medical Research . 2019 Jul; 6(7): 61-63
18. Pluchino N, Drakopoulos P, Wenger JM, Petignat P, Streuli I, Genazzani AR. Hormonal causes of recurrent pregnancy loss (RPL). Hormones (Athens). 2014 Jul-Sep;13(3):314-22

19. Royal College of Obstetricians &Gynaecologists . *The Investigation and Treatment of Couples with Recurrent First-Trimester and Second Trimester Miscarriage.* Royal College of Obstetricians &Gynaecologists; London, UK: 2011. Guideline No. 17.

20. Dimitriadis E., Menkhorst E., Saito S., Kutteh W.H., Brosens J.J. Recurrent pregnancy loss. *Nat. Rev. Dis. Prim.* 2020;6:98.

21. Negro R., Stagnaro-Green A. Clinical Aspects of Hyperthyroidism, Hypothyroidism, and Thyroid Screening in Pregnancy. *Endocr. Pract.* 2014; 20:597–607.

22. Dhillon-Smith R.K., Middleton L.J., Sunner K.K., Cheed V., Baker K., Farrell-Carver S., Bender-Atik R., Agrawal R., Bhatia K., Edi-Osagie E., et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. *N. Engl. J. Med.* 2019;380:1316–1325.

23. Coomarasamy A., Dhillon-Smith R.K., Papadopoulou A., Al-Memar M., Brewin J., Abrahams V.M., Maheshwari A., Christiansen O.B., Stephenson M.D., Goddijn M., et al. Recurrent miscarriage: Evidence to accelerate action. *Lancet*. 2021;397:1675–1682. doi: 10.1016/S0140-6736(21)00681-4.

24. Duane M., Schliep K., Porucznik C.A., Najmabadi S., Stanford J.B. Does a short luteal phase correlate with an increased risk of miscarriage? A cohort study. *BMC Pregnancy Childbirth.* 2022;22:922

25. Toth B., Würfel W., Bohlmann M., Zschocke J., Rudnik-Schöneborn S., Nawroth F., Schleußner E., Rogenhofer N., Wischmann T., von Wolff M., et al. Recurrent Miscarriage: Diagnostic and Therapeutic Procedures. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/ 050) *GeburtshilfeFrauenheilkd.* 2018;78:364–381. doi: 10.1055/a-0586-4568.

26. Porter MB, Brumsted JR, Sites CK. Effect of prolactin on follicle-stimulatinghormone receptor binding and progesterone production in culturedporcine granulosa cells. Fertil Steril 2000;73:99-105.

27. Li W, Ma N, Laird SM, Ledger WL, Li TC. The relationship betweenserum prolactin concentration and pregnancy outcome in women withunexplained recurrent miscarriage. J Obstet Gynaecol 2013;33:285-8.

28. Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H.Hyperprolactinemic recurrent miscarriage and results of randomizedbromocriptine treatment trials. Fertil Steril 1998;70:246-52

29. Ali S, Majid S, Ali N., Taing S, El-Serehy HA, Al-Misned FA. Evaluation of etiology and pregnancy outcome in recurrent miscarriage patients. *Saudi J. Biol. Sci.* 2020;27:2809–2817. doi: 10.1016/ j.sjbs.2020.06.049.

30. Vomstein K., Feil K., Strobel L., Aulitzky A., Hofer-Tollinger S., Kuon R.-J., Toth B. Immunological Risk Factors in Recurrent Pregnancy Loss: Guidelines Versus Current State of the Art. *J. Clin. Med.* 2021;10:869.

31. Cao Y., Wang X., Cao Z., Cheng X. Association of Vitamin D receptor gene TaqI polymorphisms with tuberculosis suscep-tibility: A meta-analysis. *Int. J. Clin. Exp. Med.* 2015;8:10187–10203.

32. Terzic M., Aimagambetova G. *Management of Infertility: A Practical Approach.* Academic Press; Cambridge, MA, USA: 2023. Prothrombotic gene polymorphisms and adverse reproductive outcomes in assisted reproductive technology; pp. 55–63.

33. Alecsandru D., Klimczak A.M., Velasco J.A.G., Pirtea P., Franasiak J.M. Immunologic causes and thrombophilia in recurrent pregnancy loss. *Fertil. Steril.* 2021;115:561–566.

34. Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol. 2009 Spring;2(2):76-83.

35. Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. *Fertil Steril.* 1996;66:24–29.

36. Fox-Lee L, Schust DJ. Recurrent pregnancy loss. In: Berek JS, editor. *Berek and Novak's Gynecology.* Philadelphia: Lippincott Williams & Wilkins; 2007. pp. 1277–1322.

37. Hady El Hachem, Vincent Crepaux, Pascale May-Panloup, Philippe Descamps, Guillaume Legendre & Pierre-Emmanuel Bouet (2017)

Recurrent pregnancy loss: current perspectives, International Journal of Women's Health, 331-345,

38. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006 Jul;91(7):2587-91.
39. Otani T, Roche M, Mizuike M, Colls P, Escudero T, Munné S. Preimplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. Reprod Biomed Online. 2006 Dec;13(6):869-74.
40. 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: index [corrected]-control study. BMJ. 2006 Apr 01;332(7544):759-63.
41. Akhtar MA, Saravelos SH, Li TC, Jayaprakasan K, on behalf of the Royal College of Obstetricians and Gynaecologists. Reproductive Implications and Management of Congenital Uterine Anomalies. Scientific Impact Paper No. 62. *BJOG* 2020; 127: e1–e13.
42. Hamulyák EN, Scheres LJJ, Goddijn M, Middeldorp S. Antithrombotic therapy to prevent recurrent pregnancy loss in antiphospholipid syndrome-What is the evidence? J ThrombHaemost. 2021 May;19(5):1174-1185.
43. Toth B, Vomstein K, Togawa R, Böttcher B, Hudalla H, Strowitzki T, Daniel V, Kuon RJ. The impact of previous live births on peripheral and uterine natural killer cells in patients with recurrent miscarriage. Reprod Biol Endocrinol. 2019 Aug 31;17(1):72.
44. Dakhly DM, Bayoumi YA, Sharkawy M, Gad Allah SH, Hassan MA, Gouda HM, Hashem AT, Hatem DL, Ahmed MF, El-Khayat W. Intralipid supplementation in women with recurrent spontaneous abortion and elevated levels of natural killer cells. Int J Gynaecol Obstet. 2016 Dec;135(3):324-327.
45. Rasmark Roepke E, Hellgren M, Hjertberg R, Blomqvist L, Matthiesen L, Henic E, Lalitkumar S, Strandell A. Treatment efficacy for idiopathic recurrent pregnancy loss - a systematic review and meta-analyses. Acta ObstetGynecol Scand. 2018 Aug;97(8):921-94