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An Overview of Therapeutic Management of Recurrent Pregnancy Loss

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Review Article

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Abstract

Recurrent Pregnancy loss is defined as three or more consecutive pregnancy losses before 20 wks gestation. Usually causes are found in 70-80% of cases as chromosomal, anatomical defects, thrombophilias-both acquired and inherited, endocrine. But in 20-30% no definite cause is found. We searched electronic databases Pubmed from 1950-2016 using different keywords. As for the diagnosis, management remains controversial. Here we review the basis of use of various kinds of therapies like progesterone, low molecular weight heparin, aspirin, intravenous immunoglobulin, intra lipid therapy and steroids for routine use in RPL and is empiric use of these agents justified.

Keywords: RPL; Antiphospholipid syndrome; Low molecular weight heparin; IV Immunoglobulin; Intralipid therapy; Unexplained

Abbreviations: RPL: Recurrent Pregnancy Loss; APS: Antiphospholipid Syndrome; d RVVT: Dilute Russell Viper Venom Time; APS: Anti Cardiolipin; TABLET: Thyroid Antibody and Levothyroxine Study

Introduction

Recurrent miscarriages as defined by WHO, is three or more consecutive involuntary termination of pregnancy before 20 wks of gestation or below 500g fetal weight. Losses later after 20wks are considered still births or premature births and have different aetiologies [1]. ASRM practice committee defines recurrent pregnancy loss (RPL) as 2 or more failed clinical pregnancies [2]. The risk of abortion after 2 repeated losses is 17-25%,while after 3 consecutive losses is 25-46%.This gets worsened with increasing women's age [3]. Also incidence has been found to be higher in infertile women with recurrent spontaneous miscarriage as compared to general population [4]. Self reported losses cannot be relied on, while only 71% of such clinical losses were checked in hospital record [5]. Thus there is importance of defining pregnancy as a clinical pregnancy documented on USG or HPE. This review attempts to highlight the update in the etiology and management of RPL.

Investigations

History

Past obstetric history is important. Secondary infertility is a feature of RM. Embryonic vital signs in preceding pregnancies are prognostic markers and need to be regarded as a strong compounding factor in trials on therapeutic intervals [6].

Genetic

The incidence of chromosome abnormalities in women undergoing single sporadic miscarriages is 45% [7]. Roughly 50-60% of early spontaneous abortions are associated with chromosomal anomaly of the conceptus. Aneuploidy is the commonest abnormality along with autosomal trisomy which accounts for >50% of abortuses having a chromosomal anomaly [8]. Since parental karyotyping does not predict a subsequent miscarriage [9], it is not advised to carry out routine karyotyping for those couples having RM. Importance of cytogenetic analysis of POC is that if it is shown that there is aneuploid foetus it indicates a higher chance of having successful feature pregnancy [9].

Uterine Defects

There is 3.2 -6.9%chance of having a major uterine defect in women with RPL, while the incidence of arcuate uterus is 1%-11.9% [10]. USG is the easily present cheap measure which does not cause radiation exposure. 2D USG can pick up half of uterine congenital anomalies but has very low false positive rates [11]. According to some combining hysteroscopy and laparoscopy can be the gold standard in evaluating congenital uterine anomalies [12-15]. Yet these are invasive tests.3D USG in experienced hands has more accuracy than 2D USG and equal to MRI at determining uterine anomaly [16]. Sonohysterongraphy is a non invasive method having 95%chance of identifying uterine anomalies MRI is a very sensitive and specific method available because of its higher ability to reliably see complex anomalies in uterus and vagina [17,18]. One can use 2D USG for initial screening. Combined Hysteroscopy and laparoscopy, sonohysterography, MRI and 3D USG can be left to make a confirmatory diagnosis.

Infections-Just like bacterial vaginosis is a risk factor for preterm delivery, similarly it carries strong risk of inducing late miscarriages [19]. Therefore vaginal swabs should be considered to screen women having previous history of late miscarriage [20]. Other than toxoplasma there is no indication of TORCH testing [21].

Haematological Problems

Acquired Thrombophilia

Antiphospholipid syndrome (APS) is auto immune disorders which -> a hypercoagulable state. It is the only thrombophilia which has proved to have association in influencing bad pregnancy outcomes [22]. Clininically this disorder is characterized by any thrombotic event and or specific obstetric complications, like preterm delivery and recurrent miscarriages.5-15% of women with RPL Have clinically important APL antibody titres in contrast to 2-5% of unselected obstetrical patients Apart from clinical symptoms the presence of persistence circulating antiphospholipid antibodies (APL) is used for the diagnosis of APS with reported incidence of 8-42%. APL's are heterogeneous family of auto antibodies against proteins binding to negatively charged phospholipids [23-25]. They cause thrombogenic effects since they interfere with plasmatic components of the coagulation cascade, stimulate platelet aggregation and cause a proinflammatory and procoagulant endothelial phenotype [26]. Normally the importance of APL which are diagnostic are IgG or IgM isotype antibodies directed against-β-2 glycoprotein (anti-β2GPI)and cardiolipin antibody (ACL) usually combined with dilute Russell viper venom time(d RVVT)panel for detecting lupus anticoagulant (LA) in those patients at high risk of thrombosis and an LA insensitive a PTTK [27,28]. Patients with a triple positivity are thought to be at higher risk than those with single or double positivity in developing vascular thrombosis pregnancy morbidity and recurrent event [29,30]. The lupus anticoagulant test is most predictive for venous arterial thrombosis in patients with suspected APS, while a high inter method variability for ACL assay exist. This shows low utility of ACL testing [31,32]. The diagnostic value of the major epitope of β2GPI is still controversial due to potential conformational changes during the immune assay which may=>epitope masking effects. Hence there is no universal ACL detection method [33]. At present the diagnosis of APS requires the detection of at least one of the 3 APL ie IgG or IgM Isotype antibodies directed against beta 2 glycoprotein1 (antiβ2GPI) and cardiolipin (ACL) or a positive lupus anticoagulant (LA) functional assay. Additionally the revised Sapporo' criteria provides important details about the titre (>40GPI or MPL) or >99th percentile for ACL and >99th percentile antibeta 2GPI) of APL and their persistence in time (present on 2 or more occasions at least 12wks apart)to decrease the probability of misdiagnosing. APS in patients with thrombosis or pregnancy morbidity with transient or low titre APL antibodies [29]. Further there is emerging group of auto antibodies potentially associated with APS [34]. These auto antibodies are directed against proteins involved with coagulation, or cell membrane binding but their clinical utility and diagnostic value remain unclear. This => a diagnostic gap in patients with clinical symptoms of an APS but without evidence of established serological markers (seronegative APS, SNAPS) may have fatal consequences for the patients. International consensus classification criteria for diagnosis of APS are based on presence of at least one of the clinical criteria which

include vascular thrombosis or pregnancy morbidity. Having one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, severe preeclampsia or eclampsia, recognized feature of placental insufficiency before 34th wk GA and 3 or more unexplained consequent spontaneous abortions prior to 10th wkGA constitute features of pregnancy morbidity. Any one of APS clinical features with abnormal lab test diagnosis APS .When patient has CF's of APS but negative APL assay possibility of seronegative APS is there. Non criteria test such as ACL, Beta 2GP IgG Ab's and antiphosphatidyl serine antibodies may help to clarify the picture. It was shown by Ruffatti that pregnant women with APS reported that pts with triple APL Ab positivity (i.e positive for LA, ACL and anti-beta 2GPI Ab's and/or post thromboembolism has a greater likelihood of poor neonatal outcomes as compared to pts with single or double APLAb positivity and no history of thrombosis [35]. While other studies showed that lupus anticoagulant is the primary predictor of adverse pregnancy outcomes in APL associated pregnancies [36]. In a case with 6 RPL and fulminant stroke Scholtz et al. found presence of auto antibodies against annexins, potentially associated with APS .Using immunoassays, immunoblots to detect auto antibodies directed against A1-5 and A8 respectively in a patient seronegative for APL they found strong IgM isotype Ab reactivity directed against annexin A1,3 and 5. Further studies are needed to evaluate the diagnostic value of IgM isotype Ab's against A1-5 and A8 for seronegative and recurrent miscarriages [37]. Another case was reported of bilateral sudden hearing loss following RPL associated with APS as a first manifestation of APS [38].

Inherited Thrombophilia

Inherited thrombophilia like factor V laden mutation, prothrombin gene mutation (PT20210A) and deficiencies of natural protein C, protein S and antithrombin are associated with recurrent miscarriages (RM) [39]. That these heritable thrombophilias and pregnancy cause pregnancy failure is controversial. Combination of various risk factors like multiple inherited thrombophilic defects=> secondary hypercoagulable state [40]. There is moderate association (odds ratio2to3) between RM and thrombophilias like factor V laden mutation and the prothrombin G20210A mutation [41]. But this risk is stronger for fetal deaths like still births following 20wksthan RPL. Other large prospective studies do not show association between thrombophilas and sporadic pregnancy loss [42-45]. Thus with no strong correlation role of use of anticoagulants for increasing likelihood of live birth is not documented [45]. Disadvantage of testing pts with VTE for throbophilias is the high cost for testing .Thus there is no role of routine thrombophilia testing in women with RPL [45].

Methyl Tetrahydrofolate Reductase (MTHFR) Mutation

This is an important enzyme which catalyzes the conversion of 5,10methylene tetra hydrofolate which is the important circulating form of folate [46]. MTHFR gene polymorphisms are usually associated with hyperhomocysteinemia [47,48]. Hence hyperhomocysteinemia is considered a risk factor for neural tube defects [NTD [49,50] and recurrent embryo loss [50,51]. Homocysteine levels fluctuate based on a person's individual state on measurement (based on intake of folic acid, vit B1 2) hence it is not easy to get dependable results. Mild hyperhomocysteinemia has been found to be a risk factor for arterial disease and venous thrombosis. There is no definitive importance of hyperhomocysteinemia in RM causation [52,53]. Thus routine testing of MTHFR mutation is not a part of routine evaluation OF RM.

Endocrine

PCO is the commonest identified USG change in women having RM [54]. Incidence of PCO's is 40% in women with RM, yet only on bases of polycystic morphology does not predict pregnant loss, in ovulatory women which RM conceiving spontaneously. Thus USG in pts having history of RM does not predict an adverse outcome in next pregnancy, hence is not recommended [55].

Increase Basal LH with/without PCO'S is a risk factor for miscarriage. Women having raised LH, which is an integral part of PCO'S are at greater risk for miscarriage after either spontaneous/assisted conception. Yet just decreasing endogenous LH release before conception in women with Raised circulating LH concentration and a history of RM did not improve live birth rate. There was no correlation of a SLH>10IU/L or a S. Tn >3nmol/L with raised RM rate [54].

There is an importance of insulin resistance in RM [56]. This IR may be independent of PCO status. Hyper insulinemia and high levels of PAI activity have been implicated as the promixate cause for the increased incidence of miscarriage (30-50%) observed among women with PCOS [57-59]. Metformin is an insulin sensitizing drug with proven clinical utility for ovulation induction in anovulatory women with PCOS and has been shown to decrease PAI activity [57-65]. Hence metformin treatment throughout pregnancy has been evaluated as

one means by which risk of pregnancy loss might be reduced with PCOS.

Luteal Phase Defects

Although shortened luteal phase has been associated with pregnancy loss measurements of serum progesterone levels to determine the quality of luteal function in early pregnancy and to identify pregnancies at risk which may be salvaged by support with exogenous progesterone therapy are futile. Both use of histological and biochemical end points as diagnostic criteria for endometrial dating are unreliable.

Diabetes Mellitus

Trying to test for DM should be done on clinical suspicion. Best test for diagnosing DM is the oral glucose tolerance test (OGTT) but is expensive and inconvenient. Only fasting plasma glucose might not diagnose those pts having impaired GTT. Since glycated hemoglobin does not need fasting it may be the best of the lot used for screening DM [66].

Thyroid Dysfunction

RM may be associated with both clinical and subclinical thyroid disorders. Role of TPO antibodies is controversial [67]. Pregnant women having subclinical hypothyroidism as thyroid antibodies have increased risk of RM [68,69]. TPO Ab screening is not recommended .Only thyroid function test may suffice [70].

Hyperprolactinaemia-PRL is essential for female reproduction and usually measured in women with RPL as increased PRL is associated with ovulatory dysfunction. Past in vitro studies have shown that PRL has an important role in CL maintenance and Pg production in rodents but not in humans [71]. However Pg secretion by cultured granulose cells obtained from human ovarian follicles is almost completely inhibited by high PRL concentrations (100ng/ml) but not by lower conc (10-20ng/ml).Thus high PRL in early follicular growth may inhibit pg secretion=>LPD [72]. Further as reviewed in ref it is important to measure PRL levels as there might be transient hyperprolactinemia associated with unexplained infertility and RM [73,74].

Immunology

Lot of RPL is associated with immune aetiologies different aetiologies are possible. Peripheral natural killer cells and uterine NK cells have been associated with reproductive failure. Abnormally functioning immunocompetent cells including NK cells in the endometrium are thought to be responsible and treatment trial with oral prednisolone and IVIgG's are now underway [75,76]. Peripheral immunological dysfunction is observed in RM [77]. Chronic histiocytic intervillositis is a rare type of placental pathology, which is associated with reproductive loss and has an immune aetiology [78]. There are various studies which suggest that women having RPL has exaggerated inflammatory immune response both before and during pregnancy and signs of breakage of tolerance to auto Ag's and fetal Ag's occurs [79]. Neither there is standardization of counting uterine NK cells nor any agreement as to what is an abnormal level [76]. Hence the value of measuring pNK/uNKcell parameters is uncertain. No immunological test is recommended at present for RM investigations.

Male Factors

-There is increased sperm DNA fragmentation found in semen samples of couples with RPL [80-82]. A metanalysis determined a marked increase in miscarriage in patients with high DNA damage compared with those with low DNA damage [83]. Various tests are available for assaying sperm quality, of these terminal uridine nick end labeling assay (TUNEL), sperm chromatin structure Assay(SCSA), sperm chromatin dispersion(SCD)and alkaline Comet assay. Of these alkaline Comet assay showed a better prediction for male fertility [84]. 15.2%men with azoospermia had a chromosomal abnormality while 2.3% non azoospermic men also had the same. Abnormality of male factors accounts significantly for RPL after assisted conception. Number of azoospermic men who are required to be screened to prevent miscarriages is 80-88and the number needed to screen is 315-347for those who are non azoospermic [85]. Although some evidence shows association between DNA fragmentation and RM, well designed prospective studies are required before using these tests in clinical practice [86]. Routine tests for spermiploidy (e.g fluorescence in situ hybridization (FISH) or DNA fragmentation is not recommended.

Management

Lifestyle Advices

Since cause of RM can be found only in roughly 50-60% there is marked psychological impact of RM [87]. Hence there is need for psychological support in the form of lot of discussions and being sympathetic during counseling goes a long way in allaying anxiety. Even if no etiology is found and no treatment is started still 60-80%fetal salvage still might be expected. Hence adequate emotional support and reassurance is need [88]. Obesity, alcohol,

cigarette smoking, moderate coffee intake might be associated with sporadic miscarriage, but association with RM is not sure [81,89-91].

The Cochrane review decided that any vitamin supplementation prior to pregnancy or in early pregnancy do not prevent women experiencing miscarriage or still birth [92].

Genetic Anomalies-IVF plus prenatal genetic technique is a suggested way of trying to treat couple shaving chromosomal abnormalities and RM [93]. This is thought to be a faster method of trying to get a live child than natural conception at least for translocation carriers with RM [94]. Yet this is questioned. Systemic review shave shown that there is no definitive evidence to vouch for prenatal genetic screening for both unexplained RM as well as structural chromosome. Abnormalities New techniques like trophectoderm laser assisted blastocyst biopsy and molecular karyotyping via whole genome amplification and either comparative genomic hybridization(CGH)or single nucleotide polymorphism(SNP)arrays helped to revitalize the concept of preimplantation genetic screening as a treatment of RM is not recommended [93,95,96].

Anatomical Defects

It is seen that 65-85% of patients with septate uteri have a successful pregnancy outcome after metroplasty. Yet 59.5% of pts with such anomalies get a successful subsequent pregnancy without surgery giving a total live birth rate of 78%.Thus greater evidence is required for justification of metroplasty in these women [10]. Similarly clinical management of pregnancy loss patients with asherman's syndrome, uterine fibroids is controversial with no definitive evidence that surgical treatment decreases the risk of pregnancy loss. Hence minimally invasive surgeries are the better option for treatment of structural defects. Usually cervical incompetence is treated with cervical encerclage, yet the CERVO trial did not show any benefit of cerclage There is indication of doing trans vaginal USG during pregnancy in history of midterm loss due to cervical incompetence [97]. New data indicate that emergency cerclage is associated with a longer latency and period giving a better pregnancy outcome as compared to bed rest [98]. Clinical length doesn't effectively predict preterm delivery [99]. Shirodhkar technique of cerclage was found to be superior to Mc donald one for prolongation of pregnancy in a singleton pregnancy undergoing USG indicated cerclage [100]. Cerclage, vaginal Pg or pessary are found to have equal efficacy in the prevention of preterm labour in women having short cervix seen on USG during the mid trimester in single pregnancy [101,102].

Infection

Treatment of asymptomatic abnormal vaginal flora along with bacterial vaginosis with clindamycin in early 2nd trimester markedly reduces the rate of late miscarriage, and spontaneous preterm birth in a general obstetric population [20,103].

Endocrine Disorders

Any endocrine disorder in mother, be it DM, thyroid dysfunction needs to be examined [104,105]. Despite elevated LH being associated with increased risk of miscarriage, suppression of LH with GnRH agonist before ovulation induction did not give any different outcomes. In case of hyperprolactinemia, normalization of PRL levels by a dopamine agonist (bromocriptine, cabergoline) improved subsequent pregnancy outcomes in pts with RPL [106,107]. For thyroid disorders one can treat medically to get euthyroid status with eltroxine for hypothyroidism and propylthiouracil for hyperthyroidism and modify doses with pregnancy appropriately. There is a debate about what constitutes a normal TSH. There is an emerging view that TSH>2.5Miu/l is outside normal range [3]. Requirement of TH in early pregnancy is greater. Some evidence shows association of raised TPO thyroid antibodies with RM [75,108]. Levothyroxine 50µgod for women with raised TPO Ab's with normal TSH is suggested for this. Some studies show that TPO Ab positive status does not have a prognostic value regarding the subsequent outcome of a consecutive pregnancy and use of empirical eltroxine for those who were positive did not seem to improve outcome [67]. In the TABLET (thyroid antibody and levothyroxine study), A RCT of the efficacy and mechanism of levothyroxine treatment in pregnancy and neonatal outcomes in women with thyroid Ab's. This study will guide to the role of levothyroxine in such pts.

Till good evidence is available T4 therapy is not recommended for raised thyroid antibodies in pt having normal TFT.

Progesterone Stimulation

Pg causes a change of proinflammatory TH1 cytokines to anti-inflammatory TH2 cytokines response which is a more favorable pregnancy protective [109,110]. Dihydrogesterone is a potential immune modulator, which produces Pg induced blocking factor (PIBF), a

protein made up by lymphocytes on Pg exposure. PIBF inhibits cell mediated cytotoxicity and natural killer cell activity. Hence it is immune protective for Pg. Giving Pg to women with sporadic abortions is not effective [111-113]. There is a large multicentre study known as promise study (http///wwwmedscinet), which is underway to assist benefits of Pg supplementation in women with unexplained RM. Commonest regimen used is micronized Pg 400mg OD orally or vaginally however the structural formulation of dydrogesterone gives it some superiority in RM. Since there is no harm and some benefits, decision to use it should be individualized.

Metformin-There is contradictory data on use of metformin for decreasing chances of miscarriage. Although IR is an independent risk factor for spontaneous miscarriages in pregnancy patients with IR need to be advised regarding improving their insulin sensitivity through lifestyle changes or medical intervention before infertility treatment to decrease the risk of spontaneous miscarriages. Various nonrandomized studies have demonstrated that use of metformin in insulin resistance people may decrease miscarriage risk by restoring normal homeostasis and improving endometrial milieu [114,115].

Hematological Disorders

APS-Use of low dose acetyl salicylic acid and low molecular weight heparin (LMWH) are effective in decreasing miscarriages by 54%. Yet role of LMWH and aspirin treatment specifically and or RM prevention is controversial. Metaanalysis showed combination of unfractionated heparin and aspirin gives a significant benefit in live birth. Heparin prevents complement activation in pregnant patients with APL Ab'S [116]. The complex consisting of heparin binding epidermal growth factor has been shown to facilitate an invasive phenotype of the thromboplast and inhibits apoptosis [116]. Heparin also increases free levels of IGF1 and IGF2, which increases trophoblast invasion [117]. Heparin has been shown to induce transcription of matrix metalloproteinases which is known to regulate cell-cell interactions including breakdown of the deiduas basement membrane, facilitates trophoblast invasion. However efficacy of LMWH remains unproven as LMWH data were based only on 2 trials. These trials were criticized as studies were not blinded and the randomization procedure had been criticized in one of the trials and inclusion criteria were very different.3rd trial showed no significant differences in live birth rate with LMWH treatment and aspirin in women with RM [118]. A small trial showed comparative results with LMWH and aspirin using as alternative to unfractionated heparin and aspirin in the management of RM, Secondary to APS [119]. It is agreed that combination of LMWH and aspirin is superior to aspirin alone in achieving more live births. Hence it is recommended treatment for RM with APS [120,121]. Glucocorticoids are to be avoided in APS without connective tissue disorder. Low dose prednisone can be used if lupus is present along with advice of rheumatologist. Prednisone does not prevent recurrent fetal deaths in women with APLAb's [122]. In women having history of thrombosis with APS or heritable thrombophilia if diagnosed should get an ideal dose of unfractionated heparin/LMWH [23].

Inherited Thrombophilia

Here role of anticoagulant therapy is questionable. Few studies reveal that LMWH therapy during pregnancy may improve the live birth rates of women with RM in 2nd trimester associated with inherited thrombophilia [123-125]. Yet right now there is no evidence supporting treatment as observation research is hampered by poor methodology or inconsistent results [126]. A metanalysis showed that use of LMWH in pts with inherited thrombophilia with RPL is not indicated [127]. Thus one needs to follow these women with thrombophilia closely without routine prophylactic LMWH and only use for prevention of venous thromboembolism in limited cases.

Hyperhomocysteinemia

Use of high doses of folic acid (5mg) and Vit B12 (0.5mg) od has been shown to decrease homocysteine levels, but a RCT on effects of different doses of both vitamins on pregnancy has not been conducted. One can consider high doses of FA in women with high BMI, DM.

Immunotherapy-Both organ specific and systemic autoimmunity is related to greater incidence of RM. Mechanisms of possible efficacy of high dose intravenous immunoglobulin (iv IgG) therapy might include enhancement of CD94 expression and subsequent suppression of NK/Cell cytotoxicity [128]. However recent metaanalysis did not support the role of routine iv IgG. Similarly there is no evidence supporting routine use of intralipid therapy [129]. Intralipid is a fat emulsion made from soyabean oil, glycerine and egg phospholipids, normally used for parenteral nutrition in patients not able to consume orally. Various strategies including paternal cell immunization, 3rd party donor leukocytes, trophoblast membranes and iv IgG have been tried but none of them proved to be of benefit over placebo in improving the LBR [130]. There has been a lot of criticism of Cochrane

review as the essential sub analysis between primary and secondary recurrent miscarriages. Metaanalysis showed that IV IgG increased rate of live birth in secondary RM, but insufficient data was there for it being used for primary RM [131,132]. Also there is risk of possible complications like undesirable immune response and possibility of transmitting infectious disease like cytomegalovirus. Although this risk of transmitting infection is very small. Recent systemic review and analysis concluded that NK cell analysis and immune therapy should be offered only for clinical research [133] and current recommendation is for not advising immunotherapy [130]

Unexplained Recurrent Miscarriage

Psychological Support: Since stress is a risk factor for miscarriages and RM is a stressful condition so one needs to break this vicious cycle by strong psychological support. Thus reassurance of women for a successful future pregnancy with supportive care is needed [134].

Aspirin: There is no definitive evidence for use of aspirin (75mgod) in treatment of RM in women without APS. Recent trials failed to support role of aspirin in unexplained RM [135]. Aspirin is useful in many undiagnosed implantation failures.

Progesterone: A metaanalysis of 4 RCT's and only 132 women in total showed a statistically significant reduction in miscarriages [136]. Further evidence is awaited before making recommendation on use of Pg in unexplained RM.

LMWH: There is no role of LMWH for preventing RM in the absence of APS

HCG: A Cochrane review carried out recently failed to find any evidence to support use of HCG in preventing miscarriages [137]. Hence routine use of HCG is not recommended.

Steroids: Effect of prednisolone therapy in some women with RM may be due to altered endometrial angiogenesis, growth factor expression and reduced blood vessel maturation [138]. But role is limited to RM having known connective tissue disorder aetiology. The results for the prednisolone trials are awaited. It is a RCT of prednisone for women with idiopathic RM's and raised uNK cells in the endometrium [139]. There is no strong evidence to recommend its use in unexplained RM.

Immunoglobulin: IVIg for treatment of unexplained RM is not justified.

Intralipid Solution: There is no evidence of benefit with the use of intra lipid solution. Well controlled large scale and confirmatory studies are needed to see if it can be recommended for use [129,140].

Conclusion

RM might be the first presentation of some of the hematological/endocrine disorder. A lot of investigations like genetic thrombophilia screening are not based on strong evidence. Management of unexplained RM remains a challenge. Role of LMWH and aspirin are controversial in genetic thrombophilias. There is no role for immunotherapy or intralipid therapy at present. Consanguity is another risk factor for structural chromosomal abnormalities besides higher incidence of factor V Leiden and prothrombin A20210G Polymorphisms [141,142].

References

1. WHO (1977) WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as attended Oct 14 1976. Acta Obstet Gynecol Scand 56(3): 247-253.

2. Practice Committee of the American Society for Reproductive Medicine (2012) Evaluation and treatment of recurrent pregnancy loss: A committee opinion. Fertil Steril 98(5): 1103-1111.

3. Regan L, Braude PR, Trempath PL (1989) Influence of past reproductive performance on risk of spontaneous abortion. BMJ 299(6698): 541-545.

4. Coulam CB (1992) Association between infertility and spontaneous abortion. Am J Reprod Immunol 27(3-4): 128-129.

5. Christiansen OB, Nybo Andersen AM, Bosch E, DayaS, Delves PJ, et al. (2005) Evidence based investigations and treatment of recurrent pregnancy loss. Fertil Steril 83(4): 821-839.

6. Van den Berg MM, Van MaaDrle MC, Van Wely M, Goddijn M (2012) Genetics of early miscarriage .Biochim Biophys Acta 1822(12): 1951-1959.

7. King C, Magez J, Hedderech J, Von Otte S, Kabelitz (2016) Two year outcome after recurrent first trimester miscarriages: prognostic value of the past obstetric history. Arch Gynecol Obstet 293(5): 1113-1123.

8. Lathi RB, Gray Hazard FK, Herema-McKenney AM, TaylorJ, Chueh JT (2011) First trimester miscarriage evaluation. Semin Reprod Med 29(6): 463-469.

9. Carp H, Guetta E, Dorf H, Soriano D, Barkai G, et al. (2006) Embryonic karyotype in recurrent miscarriage with parental karyotypic lterations. Fertil Steril 85(2): 446-450.

10. Sugiura–Ogasawra M, Ozaki Y, Katano K, Suzumori N, Mizutani E (2011) Uterine anomaly and recurrent pregnancy loss. Semin Reprod Med 29(6): 514-521.

11. Saravelos SH, Cocksedge KA, Li TC (2008) Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: Acritical appraisal. Hum Reprod Update 14(5): 415-429.

12. Hamilton J, Larson AJ, Lower AM, HasnainS, Grudzinskas JG (1998) Routine use of saline hystersonography in 500 consecutive, unselected, infertile women. Hum Reprod 13(9): 2463-2473.

13. Homer HA, Li TC, Cooke ID (2000) The septate uterus: A review of management and reproductive outcome. Fertil Steril 73(1): 1-14.

14. Grimbizis GF, Camus M, Tarlatazis BC, Bontis JN, Devroey P (2001) Clinical implications of uterine malformations and hysteroscopic treatment results. Hum Reprod Update 7(2): 161-174.

15. Taylor E, Gomel V (2008) The uterus and Fertility. Fertil Steril 89(1): 1-16.

16. Chandler TM, Machan LS, Coopberg PL, Harris AC, Chang SD (2009) Mullerian duct anomalies: From diagnosis to intervention. Br J Radiol 82(984): 1034-1042.

17. Ludwin A, Ludwin I, Banas T, K nafel A, Miedzyblocki M, Basta A(2011) Diagnostic accuracy of sonohysterography, hysterosalpingography and diagnostic hysteroscopy in diagnosis of arcuate, septate and bicornuate uterus. J Obstet Gynecol Res 37(3): 178-186.

18. Olpin JD, Heilbrun M (2009) Imaging of mullerian duct anomalies. Clin Obstet Gynecol 52(1): 40-56.

19. Leitich H, Kiss H (2007) Asymptomatic bacterial vaginosis and intermediate flora a risk factors for adverse pregnancy outcome. Best Practt Res Clin Obstet Gynecol 21(3): 375-390.

20. Kochar Kaur K, Allahbadia GN, Singh M (2012) Role of TORCH in INFERTILITY: a review with special emphasis on toxoplasmosis with pregnancy. pp.1-23

21. Wilkowska–Trojniel M, Zdrodowska-Stefanow B, Ostazewska-Puchalska I, Redzko S, Przepiesc J, et al. (2009) The influence of Chlamydia trachomatisn infection on spontaneous abortion. Adv Med Sci 54(1): 86-90.

22. Mc Namee K, Dawood F, Farquharson R (2012) Recurrent miscarriage and thrombophilia: An update. Curr Opin Obstet Gynecol 24(4): 229-234.

23. Branch DW, Gibson M, Silver RM (2010) Recurrent miscarriage. N Engl J Med 363(18): 1740-1747.

24. Yetman DL, Kutteh WH (1996) Antiphospholipid antibody panels and recurrent pregnancy loss: Prevalence of anticardiolipin antibodies compared with other antiphospholipid antibodies. Fertil Steril 66(4): 540-546.

25. American College of Obstetricians and Gynaecologists Committee on Practice Bulletin No 118 (2011) Antiphospholipid Syndrome. Obstet Gynecol 117(1): 192-199.

26. Meri PL, Borghi MO, Raschi E, Tedesco F (2011) Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol 7(6): 330-339.

27. Galli M, Finazzi G, Bevers EM, Barbui T (1995) Kaolin clotting time and dilute Russell's viper venom time distinguish between prothrombin dependent and beta 2-glycoprotein 1-dependent antiphospholipid antibodies. Blood 86(2): 617-623.

28. Tripody A, Biasiolo A, Chantanrangkul V, Pengo V (2003) Lupus anticoagulant (LA) testing: Performance of clinical laboratories assessed by a national survey using lyophilized affinity-purified immunoglobulin with LA activity. Clin Chem 49(10): 1608-1614.

29. Galli M (2010) The antiphospholipid triangle. J Thromb Haemost 8(2): 234-236.

30. Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, Erba N, et al. (2010) Clinical course of high risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 8(2): 237-242.

31. Devreese KM (2012) Antiphospholipid syndrome: evaluation of the thrombotic risk. Thromb Res 130(1): S37-S40.

32. Misasi R, Capazzi A, Longo A, Recalchi S, Lococo E, et al. (2015) "New"antigenic targets and methodological approaches for refining laboratory diagnosis of antiphsphlipid syndrome. J Immunol Res 2015: 858542.

33. Chighizala CB, Gerosa M, Meroni PL (2014) New tests to detect antiphospholipid antibodies: antidomain 1 beta-2 glycoprotein 1 antibodies. Curr Rheumatol Rep 16(2): 402.

34. Forastiero R, Martinuzzo M (2015) The emerging role of multiple antiphospholipid antibodies positivity in patients with antiphospholipid syndrome. Expert Rev Clin Immunol 11(11): 1255-1263.

35. Rufatti A, Calligaro A, Hoxha A, Trevisanuto D, Ruffatti AT, et al. (2010) Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. Arthritis Care Res (Hoboken) 62(3): 302-307.

36. Lockshin MD (2013) Pregnancy with antiphospholipid syndrome. Am J Reprod Immunol 69(6): 585-587.

37. Scholz P, Auler M, Brachvogel B, Benzing T, Mallman P, et al. (2016) Detection of multiple annexin autoantibodies in a patient with recurrent miscarriages, fulminant stroke and seronegative antiphospholipid syndrome. Biochemica Medica 26(2): 272-278.

38. Yin T, Huang F, Ren J, Liu W, Chen X, et al. (2013) Bilateral sudden hearing loss following habitual abortion: a case report and review of literature. Int J Clin Exp Med 6(8): 720-723.

39. Middledorp S (2011) Is thrombophilia testing useful? Haematology Am Soc Hematol Educ Program 2011: 150-155.

40. Kutteh WH, Triplett DA (2006) Thrombophilias and recurrent pregnancy loss. Semin Reprod Med 24(1): 54-66.

41. Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, et al. (2006) Thrombophilia in pregnancy. A systematic review.Br J Haematol 132(2): 171-196.

42. Dizon-Townson D, Miller C, Sibai P, Spong CY, Thom E, et al. (2005) The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol 106(3): 517-524.

43. Silver RM, Zhao Y, Spong CY, Sibai P, Wendel G Jr, et al. (2010) Prothrombin gene G20210A mutation and obstetric complications. Obstet Gynecol 115(1): 14-20.

44. Said JM, Higgins JR, Moses EK, Walker SP, Borg AJ, et al. (2010) Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. Obstet Gynecol 115(1): 5-13.

45. deJong PG, Goddijn M, Middledorp S (2011) Testing for inherited thrombophilia in recurrent miscarriage. Semin Reprod Med 29(6): 540-547.

46. Zetterberg H (2004) Methyltetriahydrofolate reductase and transcobalamin genetic polymorphism in human spontaneous abortion. Biological and clinical implications. Reprod Biol Endocrino 2: 7.

47. Van der Put NM, Gabreels F, Stwvens EM, Smietnik JA, Trijbels FJ, et al. (1998) A second common mutation in the Methyltetriahydrofolate reductase gene: An additional risk factor for neural tube defects? Am J Hum Genet 62(5): 1044-1051.

48. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, et al. (1995) A candidate genetic risk factor for vascular disease: A common mutation in Methyl tetriahydrofolate reductase. Nat Genet 10(1): 111-113.

49. Steegrs-Theunissen RP, Boers GH, Trijbels FJ, Eskes TK (1991) Neural tube defects and derangement of homocysteine metabolism. N Engl J Med 324(3): 199-200.

50. Steegrs-Theunissen RP, Boers GH, Blom HJ, Trijbels FJ, Eskes TK (1992) Hyperhomocysteinemia and recurrent spontaneous abortion or abruption placentae. Lancet 339(8801): 1122-1123.

51. Nelen WL, Blom HJ, Steegers EA, den Heijer M, Eskes TK (2000) Hyperhomocysteinemia and recurrent early pregnancy loss: A metaanalysis. Fertil Steril 74(6): 1196-1199.

52. Aubard Y, Darodes N, Cantaloube M (2000) Hyperhomocysteinemia and pregnancy-review of our present understanding and therapeutic implications. Eur J Obstet Gynecol Reprod Biol 93(2): 157-165.

53. Creus M, Deulofeu R, Penarrubia J, Carmona F, Balasch J (2013) Plasma homocysteine and vitamin B12 serum levels, red blood cell folate concentrations, C677T Methyltetriahydrofolate reductase gene mutation and risk for recurrent miscarriage. A case controlled study in Spain. Clin Chem Lab Med 51(3): 693-699.

54. Rai R, Backos M, Rushworth F, Regan L (2000) Polycystic ovaries and recurrent miscarriage:A reappraisal. Hum Reprod 15(3): 612-615.

55. Liddell HS, Sowden K, Farquhar CM (1997) Recurrent miscarriage: Screening for polycystic ovaries and subsequent pregnancy outcome. Aust NZ J Obstet Gynecol 37(4): 402-406.

56. Chakraborty P, Goswami SK, Rajani S, Sharma S, Kabir SN, et al. (2013) Recurrent pregnancy loss in polycystic ovary syndrome: Role of hyperhomocysteinemia and insulin resistance. PLoS One 8(5): e64446.

57. Moghetti P, Castello R, Negri C, Tosi F, Perrone E, et al. (2000) Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized double blind, placebo-controlled 6month trial, followed by open, long term clinical evaluation. J Clin Endocrinol Metab 85(1): 139-146.

58. Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS (1988) Influence of serum luteinizing hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome. Br Med J 297(6655): 1024-1026.

59. Watson H, Kiddy DS, Hamilton-Fairley D, Scanlon MJ, Barnard C, et al. (1993) Hypersecretion of luteinizing hormone and ovarian hormones in women with recurrent early miscarriage. Hum Reprod 8(6): 829-833.

60. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R (1998) Effects of metformin on spontaneous and clomiphene induced ovulationin the polycystic ovary syndrome. N Engl J Med 338(26): 1876-1880.

61. Velazquez E, Acosta A, Mendoza SG (1997) Menstrual cyclicity after metform in therapy in polycystic ovary syndrome. Obstet Gynecol 90(3): 392-395.

62. Glueck CJ, Wang P, Fontaine R, Sieve SmithL, Tracy T, et al. (1999) Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy with polycystic ovary syndrome. Metabolism 48(12): 158-159.

63. Velazquez EM, Mendoza SG, Wang P, Glueck CJ (1997) Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoproteina and immunereactive insulin levels in patients with the polycystic ovary syndrome. Metabolism 46(4): 454-457.

64. Atiomo WU, Bates SA, Condon JE, Shaw S, West JH, et al. (1998) The plasminogen activator system in women with polycystic ovary syndrome. Fertil Steril 69(2): 236-241.

65. Sampson M, Kong C, Patel A, Unwin R, Jacobs H (1996) Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without polycystic ovary syndrome. Clin Endocrinol 45(5): 623-629.

66. Malkani S, DeSilva T (2012) Controversies on how diabetes is diagnosed. Curr Opin Endocrinol Diabetes Obe Reglias 19(2): 97-103.

67. Yan J, Sripada S, Saravelos SH, C n ZJ, Egner W, et al. (2012) Thyroid peroxidase antibody in women with unexplained recurrent miscarriage: Prevalence, prognostic value, and response to empirical thyroxine therapy. Fertil Steril 98(2): 378-382.

68. Ticconi C, Giuliani E, Veglia M, Pietropoli A, Peiccione E, et al. (2011) Thyroid autoimmunity and recurrent miscarriage. Am J Reprod y Immunol 66(6): 452-459.

69. Pradhan M, Anand B, Singh N, Mehrotra M (2013) Thyroid peroxidase antibody in hypothyroidism: It's effect on pregnancy. J Mater Fetal Neonatal Med 26(6): 581-583.

70. Abbasi-Ghanavi M (2011) Thyroid antibodies and pregnancy outcomes. Clin Obstet Gynecol 54(3): 499-505.

71. Frasor J, Park K, Byers M, Telleria C, Kitamura T, et al. (2001) Differential roles for signal transducers and activators of transcription 5a and 5b in PRL stimulation of ER alpha and ER beta ting transcription. Mol Endocrinol 15(2): 2172-2181.

72. Porter MB, Brumsted JR, Sites CK (2000) Effect of prolactin on follicle stimulating hormone receptor binding and progesterone production in cultured porcine granulose cells. Fertil Steril 73(1): 99-105.

73. Kapil Gupta, Ramandeep Kaur (2016) Endocrine dysfunction and recurrent spontaneous abortion: An overview. Int J Basic Med Res 6(2): 79-83.

74. Bussen S, Sutterelin M, Steck T (1999) Endocrine abnormalities during the follicular phase in women with recurrent spontaneous abortion. Hum Reprod 14(1): 18-20.

75. Saito SL, Nalashima A, Shima T (2011) Future directions of studies of recurrent miscarriages associated with immune aetilologies. J Reprod Immunol 90(1): 91-95.

76. Russell P, Anderson L, Lieberman D, Tremellen K, Yilmaz H, et al. (2011) The distribution of immune cells and macrophages in the endometrium of Women with recurrent reproductive failure I: Techniques. J Reprod Immunol 91(1-2): 90-102.

77. Lissauer D, Goodyear O, Khanum R, MossPA, Kilby MD (2014) Profile of maternal CD4 T-cell effectors function during normal pregnancy and in women with a history of recurrent miscarriage. Clin Sci(Lond) 126(5): 347-354.

78. Reus AD, Van Besouw NM, Molenaar NM, Steegers EA, Visser W, et al. (2013) An immunological basis for chronic histiocytic intrvillositis in recurrent fetal loss. Am J Reprod Immunol 70(3): 230- 237.

79. Christiansen OB (2013) Reproductive immunology. Mol Immunol 55(1): 8-15.

80. Carrell DT, Liu L, Peterson CM, Jones KP, Hatasaka HH, et al. (2003) Sperm DNA fragmentation is increased in couples with unexplained recurrent pregnancy loss. Arch Androl 49(1): 49-55.

81. Brahem S, Mehdi M, Landolsi H, Moguo S, Elghezel H, et al. (2011) Semen parameters and sperm DNA fragmentation as causes of recurrent pregnancy loss. Urology 78(4): 792-796.

82. Ribas-Maynou J, Garcia-Peiro A, Fernandez-Encinas A, Amengual MJ, Prada E, et al. (2012) Double stranded sperm DNA breaks, measured by Comet assay, are associated with unexplained recurrent miscarriage in couples without a female factor. PLoS One 7(9): e44679.

83. Robinson L, Gallos ID, Conne SJ, Rajkowa M, Miller D, et al. (2012) The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod 27(10): 2908-2917.

84. Ribas-Maynou J, Fernandez–Encinas A, Garcia-Peiro A, Prada E, Abad C, et al. (2014) Human semen cryopreservation: a sperm DNA fragmentation study with alkaline and neutral Comet assay. Andrology 2(1): 83-87.

85. Dul EC, Van Echten-Arends J, Groen H, Dijkhizen T, Land JA, et al. (2012) Chromosomal abnormalities in azoospermic and nonazoospermic infertile men: Numbers needed to be screened to prevent adverse pregnancy outcomes. Hum Reprod 27(9): 2850-2856.

86. ZiniA (2011) Asperm chromatin and DNA defects relvant to the clinic? Syst Biol Reprod Med 57(1-2): 78-85.

87. Rock JA, Zacur HA (1983) The clinical management of repeated early pregnancy wastage. Fertil Steril 39(2): 123-140.

88. Stray Pederson B, Stray Pederson S (1984) Etilologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 148(2): 140-146.

89. Baird DT, Collins J, Egozcue J, Evers LH, Gianoroli L, et al. (2005) Fertility and ageing. Hum Reprod Update 11(3): 261-276.

90. Henriksen TB, Hjollund NH, Jensen TK, Bonde P, Andersen AM, et al. (2004) Alcohol consumption at the time of conception and spontaneous abortion. Am J Epidemiol 160(7): 661-667.

91. Mishra GD, Dobson AJ, Schofield MJ (2000) Cigarette smoking, menstrual symptoms and miscarriage among young women. Aust NZ J Public Health 24(4): 413-420.

92. Rumbold A, Middleton P, Pan N, Crowther CA (2011) Vitamin supplementation for preventing miscarriage. Cochrane Database Syst Rev (1): CD004073.

93. Twisk M, Mastenbroek S, Hoek A, Heineman MJ, Van der Veen F, et al. (2008) No beneficial effect of preimplantation genetic screening in women of advanced maternal age with a high risk for embryonic aneuploidy. Hum Reprod 23(12): 2813-2817.

94. Otani T, Roche M, Mizuike M, Colls P, Escuerdo T, et al. (2006) preimnplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. Reprod Biomed Online 13(6): 869-874.

95. Horne AW, Alexander CI (2005) Recurrent miscarriage. J Fam Plann Reprod Health Care 31(2): 103- 107.

96. Simpson JL (2012) Preimnplantation genetic diagnosis toimprove pregnancyoutcomes in subfertility. Best Pract Res Clin Obstet Gynecol 26(6): 805-815.

97. Brix N, Secher NJ, McCormack CD, Helmig RB, Hein M, et al. (2013) Randomised trial of cervical cerclage, with and without occlusion, for the prevention of preterm birth in women suspected for cervical insufficiency. BJOG 120(5): 613-620.

98. Namouz S, Porat S, Okun N, Windrim R, Farine D (2013) Emergency cerclage: Literature review. Obstet Gynecol Survey 68(5): 379-388.

99. Melamed N, Hiersch L, Domiz N, Maresky A, Bardin R, et al. (2013) Predictive value of cervical length in women with threatened preterm labor. Obstet Gynecol 122(6): 1279-1287.

100. Hume H, Rebarber A, Saltzman DH, Roman AS, Fox NS (2012) Ultrasound indicated circlage. Shirodhkar vs Mc Donald. J Matern Fetal Neonatal Med 25(12): 2690-2692.

101. Conde-Agudelo A, Romero A, Nicolaides K, Chaiworapongsa T, O'Brien JM, et al. (2013) Vaginal progesterone vs cervical ceclage for the prevention of pretem birth in women with a sonographic short cervix,previous preterm birth,and single gestation.A systematic review and indirect comparison metaanalysis.Am J Obstet Gynecol 208(1): 42.e1-42.e18.

102. Alfirevic Z, Owen J, Carres Moratonas E, Sharp AN, Szychowski JM, et al. (2013) Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant woman with a history of preterm birth and sonographic short cervix. Ultrasound Obstet Gynecol 41(2): 146-151.

103. Ugwumadu A, Manyonda I, Reid F, Hay P (2003) Effect of early oral clindamycinon late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: A randomized controlled trial. Lancet 361(9362): 983-988.

104. Mills JL, Simpson JL, Deiscoll SG, Jovanic-Peterson L, Van-Allen M, et al. (1988) 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 319(25): 1617-1623.

105. Hanson U, Persson B, Thunell S (1990) Relationship between hemoglobin A1C in early type 1 (insulindependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. Diabetologia 33(2): 100-104.

106. Hirahara F, Persson B, Andoh N, Sawai K, Hirabuki T, et al. (1998) Hyperprolactinaemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertil Steril 70(2): 246-252.

107. Kochar Kaur K, Allahbadia GN, Singh M (2005) How do we treat Prolactinomas in infertility.

108. Gynaecological Endoscopy and Infertility. In: Gautam Allahbadia & Rubina Merchant (Eds.), 1st (Edn.), ISBN 81-8061-506-5, Section1, Chapter 10, Jaypee brothers and Medical Publishers, India, pp: 85-96.

109. Twig G, Shina A, Amital H, Schoenfeld Y (2012) Pathogenesis of infertility and recurrent pregnancy loss. J Autoimmun 38(2-3): J275-J281.

110. Raghupathy R, Al Mutawa E, Makhseed M, Azizieh F, Szekeres-Bartho J (2005) Modulation of cytokines production by dydrogesterone in lymphocytes from women with recurrent miscarriage. BJOG 112(8): 1096-1101.

111. Raghupathy R, Al-Mutawa E, Al-Azemi M, Makhseed M, Azizieh F, et al. (2009) Progesterone induced blocking factor (PIBF) modulates cytokine production by lymphocytes from women with recurrent miscarriage or preterm delivery. J Reprod Immunol 80(1-2): 91-99.

112. Haas DM, Ramsey PS (2008) Progestogen for preventing miscarriage. Cochrane Database Syst Rev (10): CD003511.

113. Oates Whitehead RM, Haas DM, Carrier JA (2003) Progestogen for preventing Miscarriage. Cochrane Database Syst Rev 4: CD003511.

114. Daya S (1989) Efficacy of progesterone support for pregnancy in women with recurrent miscarriage. A metaanalysis of controlled trials.Br J Obstet Gyecol 96(3): 275-280.

115. Carrington B, Sacks G, Regan L (2005) Recurrent miscarriage: Pathophysiology and outcome. Curr Opin Obstet Gynecol 17(6): 591-597.

116. Glueck CJ, Streitcher P, Wang P (2002) Treatment of polycystic ovary syndrome with insulin lowering agents. Expert Opin Pharmacother 3(8): 1177-1189.

117. Berker B, Taskin S, Kahraman K, Taskin EA, Atabekoglu C, et al. (2011) The role of low molecular weight heparin in recurrent implantation failure:a prospective, quasi-randomised, controlled study. Fertil Steril 95(8): 2499-2502.

118. Nelson SM, Greer JA (2008) The potential role of heparin in assisted conception. Hum Reprod Update 14(6): 623-645.

119. Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen L, et al. (2011) Thromboprophylaxis for recurrent miscarriage in women with and without thrombophilia.HABENOX:A randomized multicentre trial. Thromb Haemost 105(2): 295-301.

120. Fouda UM, Sayed AM, Abou AM, Ramdan DI, Fouda IM, et al. (2011) Enoxaprim versus unfractionated heparin in the management of recurrent abortionsecodary to antiphospholipid syndrome. Int J Gynecol Obstet 112(3): 211-215.

121. Mak A, Cheung MW, Cheak AA, Ho RC (2010) Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive antiphospholiids: A Metaanalysis of randomized controlled trials and meta-regression. Rheumatolgy (Oxford) 49(2): 281-288.

122. Zakas PD, Pavlou M, Voulgarelis M (2010) Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: A systematic review and metaanalysis. Obstet Gynecol 115(6): 1256-1262.

123. Lockshin MD, Druzin ML, Qamar T (1989) Prednisone does not prevent recurrent fetal death in women with antiphospholipid antibody. Am J Obstet Gynecol 160(2): 439-443.

124. Carp H, Dolitzky M, Inbal A (2003) Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. J Thromb Haemost 1(3): 433-438.

125. Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J LIVE-ENOX Investigators (2005) Efficacy and safety of two doses of enoxaprim in women with thrombophilia and recurrent pregnancy loss. The LIVE ENOX study. J Thromb Haemost 3(2): 227-229.

126. Ogueh O, Chen MF, Spurli G, Benjamin A (2001) Outcome of pregnancy in women with hereditary thrombophilia. Int J Gynaecol Obstet 74(3): 247-253.

127. Kaandorp S, Di Nishio M, Goddijn M, Middledorp S (2009) Aspirin or anticoagulants for treating recurrent miscarriage in women with antiphospholipid syndrome. Cochrane Database Syst Rev 1: CD004734.

128. Tan WK, Lim SK, Tan LK, Baupista D (2012) Does low molecular weight heparin improve live birth rates in pregnant women with thrombophilic disorders. A systematic review? Singapore Med J 53(10): 659-663.

129. Shimada S, Takeda M, Nishihara J, Kaneuchi M, Sakuragi N, et al. (2009) A high dose of intravenous immunoglobulin increase CD94 expression on natural killer cells in women with recurrent spontaneous abortion. Am J Reprod Immunol 62(5): 301-307.

130. Shreeve N, Sadek K (2012) Intralipid therapy for recurrent implantation failure. New hope or false dawn?J Reprod Immunol 93(1): 38-40.

131. Porter TF, La Coursiere Y, Scott JR (2006) Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev 2: CD000112.

132. Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, et al. (2007) Use of intravenous immunoglobulin for treatment of recurrent miscarriage: A systematic Review. BJOG 1S14: 134-142.

133. Egerup P, Lindschou J, Gluud C, Christiansen OB, ImmuReM IPD Study Group (2015) The effects of intravenous immunoglobulin's in women with recurrent miscarriages: A Systematic Review of randomized trials with met-analysis including individual patient data. PLoS One 10(10): e0141588.

134. Seshadari S, Sunkarl a SK (2014) Natural killer cells in female infertility and recurrent miscarriage: A systemic review and metaanalysis. Hum Reprod Update 20(3): 429-438.

135. LiW, Newell Price J, JonesGL, L edger WL, Li TC (2012) Relationship between pshychological stress and recurrent miscarriage: ReprodBiomed Online 25(2): 180-189.

136. Kaandorp SP, Goddijn M, Van der Post JA, Hutten BA, Verhoeve HR, et al. (2010) Aspirin plus heparinor aspirin alone in wome n with recurrent miscarriage. N Engl J Med 362(17): 1586-1596.

137. Coomaramaswmy A, Truchanowicz EG, Rai R (2011) Does first trimester progesterone prophylaxis increase the live birth rate in women with unexplained recurrent miscarriage? BMJ 342: d1914.

138. Morley LC, Simpson N, Tang T (2013) Human Chorionic gonadotropin (HCG) for preventingmiscarriages. Cochrane Database Syst Rev 1: CD008611.

139. Lash GE, Bulmer JN (2011) Do uterine natural killer cells (Unk) contribute to female reproductive disorders? J Reprod Immunol 88(2): 156-164.

140. Tang AW, Alfirevic Z, Turner MA, Dury J, Que by S (2009) Prednisolone trial: Study protocol for a randomized controlled trial for prednisolone in women with idiopathic recurrent miscarriage. And raised levels of uterine natural killer cells in the endometrium. Trials 10: 102.

141. Van Dreden P, Woodhams B, Rousseau A, Favier M, Favier R (2012) Comparative evaluation of tissue factor and thrombomodulin activity changes during normal and idiopathic early and late foetal loss: The cause of hypercoagulability? Thronb Res 129(6): 787-792.

142. Turki RF, Assidi M, Banni HA, Zahed HA, Karim S, Schulten HJ, et al. (2016) Associations of recurrent miscarriages with chromosomal abnormalities, thrombophilia allelic polymorphisms and/or consanguity in Saudi Arabia. BMC Medica Genetics 17(S1): 69.