Clinical Guidelines for the Management of Recurrent Pregnancy Loss

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Executive summary

Recurrent pregnancy loss is classically defined as the occurrence of three or more consecutive pregnancy losses. American College of Obstetrician and Gynecology (ACOG) Practice Bulletin No 24 establishes testing guidelines for early recurrent pregnancy losses, as two or more consecutive losses that occurred before fifteen weeks. However, the American Society of Reproductive Medicine (ASRM) has recently redefined recurrent pregnancy losses as two or more pregnancy losses before 24 weeks. As this guideline is developed for the management of pregnancy losses in broader sector, we have adopted the ACOG definition of recurrent pregnancy losses. Although there are various terms to define repetitive pregnancy losses, for example, recurrent pregnancy losses, recurrent abortion, and habitual abortion, the working group has agreed to use the term recurrent pregnancy losses in this document.

Recurrent pregnancy lose is not only a physical condition; it involves social, psychological and spiritual domain of health as defined by WHO. Therefore a clinical guideline addressing all four domains of health is required to manage women with recurrent pregnancy losses. A clinical guideline is mandatory because it provides research-based options for decisions for the continuity of care, quality of care and a range of acceptable and accessible practices and options that can be adapted to specific needs. Clinical guidelines are increasingly used in routine health care service delivery as means of ensuring the safety of health care practices.

While the importance of clinical guidelines is well recognized, there exist some confusion regarding the nature of the aims, objectives, scopes, and target groups addressed by clinical guidelines and clinical protocols.

Clinical guidelines are systematically developed statements to assist practitioners and patient make decisions about appropriate health care for one or more specific clinical circumstances. The aim of the clinical guideline is to provide a summary and appraisal of the best available research evidence or expert consensus and highlights the strength of the evidence underlying each recommendation. The clinical guideline focuses on specific clinical circumstances and has been used by a range of stakeholders, for example clinicians, patients and third parties.

Clinical protocol is a logical flow of interventions. Clinical protocol focuses on the treatment and details recommendations that build on those made in guidelines. Unlike the broader users of the clinical guideline as enumerate above, the clinical protocol can be used only by specific clinicians.

The goal of this document is to fill in those gaps by presenting a set of principles and strategies on which recurrent pregnancy losses providers can base their care practices. The initiative for this guideline aroused from concerns raised in the recurrent pregnancy losses Working Group meetings regarding a lack of standards and guidelines in key aspects of recurrent pregnancy losses.

Although clinical guidelines have been used in health care for a long time, increasingly the processes of development of clinical guidelines have become more rigorous and transparent. In order to address bias, we have adopted the current best practice in guideline development mandates transparency; rigors and reproducibility in the guideline development process. To ensure these characteristics we have

done a rigorous literature review, organized several workshops involving various stakeholders and discussed with the team of specialists.

As recurrent lose is a social stigma, this guideline emphasizes a multidisciplinary coordinated or collaborative care approach. The multidisciplinary approach comprises the team of gynecologist, physician, counselor, psychologist and nurse.

The areas of care has been divided into six such as configuration of management of recurrent pregnancy losses, physical aspects of management of recurrent pregnancy losses, psychological aspects of management of recurrent pregnancy losses, social aspects of management of recurrent pregnancy losses, spiritual, and religious aspects of management of recurrent pregnancy losses, and cultural aspects of management of recurrent pregnancy losses. As the scope of this document was to develop a clinical guideline, we could not extensively elaborate the area 2, the physical aspect of care which is all about the clinical protocol. Together with a clinical guideline a clinical protocol is mandatory for the management of recurrent pregnancy losses, therefore we recommend for the development of a clinical protocol.

Since the medical science is ever changing, this guideline needs to be updated at 5-7 years interval to incorporate new /recent development and information in this subject. This guideline can also be access through online subscription.

Although we have made an extensive literature review it may not be an exhaustive review of all aspects of recurrent pregnancy losses care, the hope is that these guidelines can assist providers in improving service quality, and gain a broader understanding of better practices in recurrent pregnancy losses.

Background

Pregnancy loss is defined as a clinically-recognized pregnancy involuntarily ending before 24 weeks. Recurrent pregnancy loss is classically defined as the occurrence of three or more consecutive pregnancy loss.1 ACOG Practice Bulletin No 24 establishes testing guidelines for early recurrent pregnancy loss, as multiple consecutive losses that occurred before fifteen weeks gestation 2. The American Society of Reproductive Medicine (ASRM) has recently redefined recurrent pregnancy loss as two or more pregnancy losses. In reference to ACOG Nepal Society of Obstetrician and Gynecologist (NESOG) recommend the term "early recurrent abortion" for multiple consecutive losses that occurred before 15 weeks of gestation. Considering all the well recognized definitions of repeated pregnancy loss, this guideline adopted the ASRM definition in view to serve a larger population. The literature review revealed several terminologies for recurrent abortion; recurrent pregnancy loss (RPL)/recurrent abortion/habitual abortion/bad obstetric history; we propose to use the term "Recurrent pregnancy loss" in this guideline.

In addition to recurrent pregnancy loss unexplained recurrent pregnancy loss is one frequently encountered entity while managing a case of repeated pregnancy loss. Unexplained recurrent pregnancy loss is a condition where history, physical examination and all routine investigations prescribed for recurrent pregnancy loss do not reveal any abnormalities. The prognosis in these women of having a healthy pregnancy and delivering a healthy term baby is better compared to a couple with identified causes.

Several etiologies have been identified resulting in pregnancy loss. These are parental chromosomal anomalies, maternal thrombophilic disorders and structural uterine anomalies have been directly associated with recurrent miscarriage and indirectly with maternal immune dysfunction, endocrine abnormalities among others. Uterine anomaly is found in approximately 10-15% of women with recurrent miscarriage [6]. Maternal genetic mutation (2-5%); endocrine problems such as thyroid disease, are responsible for 15-20% of miscarriages, hypercoagulability,15-20% and in 0.5-5 percent of cases, infection triggers a miscarriage [6]. Older age and a history of previous miscarriages also increase the risk [7,8]. Chance of subsequent live birth among untreated with 3 previous miscarriages is about 42-86%, with 4 miscarriages is about 41-72% and with 5 miscarriages is about 23-51% [4]. Thus, the number of previous miscarriages and maternal age are the most important covariates, and they have to be taken into account when planning therapeutic trials. However, in the vast majority of cases the pathophysiology remains unknown.

Pregnancy loss including recurrent pregnancy loss is a major public health problem. It has been recorded that 12-15% of clinically recognizable pregnancies result in miscarriage [3] and 1% of fertile couples have recurrent pregnancy loss [4]. Prevalence ranges between 0.6% and 2.3% [4]. In nearly 50% of patients with RPL, the underlying cause remains unknown [5].

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While pregnancy loss is a natural part of reproduction, a pattern of two or more pregnancy loss deserves proper investigation and management. Several important issues need to be addressed in the investigation of recurrent pregnancy loss including what does it mean to a woman who has suffered recurrent pregnancy loss, what does it mean to providers caring for such women, what special consideration are necessary for managing women suffering from recurrent pregnancy loss, managing a woman who presents in the interval period when she is not pregnant – is planning pregnancy /is not planning pregnancy in near future. Similarly areas of controversies exist in the management such as cut off age of gestational age, empirical therapies, use of hormonal supplementations, extent of investigations, usefulness of TORCH, and no access to geneticist/karyotyping facilities.

The following interventions were considered but not recommended: progesterone supplementation, human chorionic gonadotrophin supplementation, prepregnancy suppression of high luteinising hormone (LH), metformin supplementation, steroid treatment, immunotherapy, serial sonographic surveillance, preimplantation genetic screening, uterine septum resection, routine TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus, and herpes simplex virus) screening. Mononuclear cell (leukocyte) immunization and IVIG are not effective in preventing recurrent pregnancy loss" (ACOG, 2001).

For most couple this evaluation can be completed in one or two months. While treatment cannot guarantee a successful pregnancy, comprehensive evaluation and treatment should result in success rates approaching 85% for most couple. Thus, a strong initiative is required to manage the burden of pregnancy loss. However, together with I/NGOs the government is focused in the management of unwanted pregnancies by and large. The government has not yet developed the definitive polices or guidelines or the management of pregnancy loss and or recurrent pregnancy loss. Keeping this in view the NESOG has taken an initiative to develop a clinical guideline for the management of recurrent pregnancy loss.

Purpose of this guideline

1. This guideline will help to set standards of care of women as Nepal Society of Obstetrics and Gynecology (NESOG) is a professional organization of technical expertise, which is committed for women's health
2. Promote evidence based ethical practices among NESOG members
3. Promote the culture of research/ education/training among NESOG members
4. Provide information to the public regarding recurrent pregnancy loss management
5. This guideline will be updated at 5-7 years interval to incorporate new /recent development and information in this subject

Target audience

1. NESOG members
2. Post graduate and undergraduate medical students –in the field of Ob/Gyn /Reproductive Health
3. Nurses

4. Undergraduate and postgraduate nursing students
5. Public Health workers
6. Counselors working with women suffering from recurrent pregnancy loss
7. Women, their family and general public interested in this subject
8. Policy makers

Methodology of developing this guideline

Topics of interest, relevance and need identified by NESOG members and executive body -------
~~2.~~1. Literature review
~~3.~~2. Working group members identified and discussion workshop
~~4.~~3. Members – Dr Kiran Regmi, Dr Anjana Karki Rayamajhi and Dr Sapana Amatya

Proposed clinical guideline for management of recurrent pregnancy loss

Area 1: Configuration of Management

Guideline 1.1 The plan of management is based on overall assessment of the woman and her family

Principle:

1. The overall assessment is multidisciplinary and well documented
2. Initial and subsequent assessments include detail history taking, review of medical records, physical examination, discussion with other providers, and laboratory tests. The initial assessment should include the woman's medico-surgical status, adequacy of diagnosis and treatment, and the result of past treatments
3. Woman and her family's educational status, expectation and understanding of the problem and prognosis, are assessed and documented
4. The assessment is reviewed on a regular basis as set by the team

Guideline 1.2 The management plan is based on the preferences, values, and needs of the woman and her family

Principal:

1. The management plan is based upon ongoing assessment of the preferences, values, and needs of the woman and her family
2. The management plan is developed after discussion with the, family, professional experts keeping in view of the existing resources
3. Management plan alternations are made in due course developed needs and outcome of the process carried out

4. The multidisciplinary team coordinates and shares the information, professional guidance for decision making, develops and carries out the management plan, and communicates management plan to the woman and her family, to all involved health professionals, and to the responsible providers when the woman transfer to different care settings
5. Treatment and care settings are clearly documented and communicated to help the woman and her family to make informed choices
6. Treatment decisions are based on assessment of risk and benefit, best evidence, and woman/family preferences.
7. Reevaluation of treatment efficacy and woman-family preferences is documented

Guideline 1.3 The multidisciplinary specialist team provides services to the woman and her family as set discussing with the woman and her family. Other therapeutic disciplines could also be included

Principle:

1. The recurrent pregnancy loss management is of at specialist-level
2. The specialist team includes obstetrician with the appropriate team to meet the physical, psychological, social, and spiritual needs of both woman and her family
3. The interdisciplinary recurrent pregnancy loss management team involved in the care of woman
4. The woman and her family have access to recurrent pregnancy loss management expertise and staff, seven days a week
5. The multidisciplinary team communicates regularly to plan, review, and evaluate the management plan, with input from both the woman and her family
6. The team meets regularly to discuss provision of quality care
7. Team members have appropriate trainings, qualifications, and experiences
8. Policies for prioritizing and responding to referrals in a timely manner are documented

Guideline 1.4 The provision for education and training is available to the multidisciplinary team

Principle:

1. Educational resources and continuing professional education focused on the domains of recurrent pregnancy loss management

Guideline 1.5 The multidisciplinary team develops, implements, and maintains evidence based recurrent pregnancy loss management

Principle:

2. The recurrent pregnancy loss management program must be committed to the highest quality of care and support for all women and their families
3. The right client should receive care at the right time
4. Woman centered care, based on the expectation and preferences of the woman and her family
5. Equitable care that is available to all in need and all who could benefit
6. Efficient care designed to meet the actual needs of the woman
7. A quality assessment and performance review is done across all the domains including organizational structure, education, team utilization, assessment and effectiveness of physical, psychological, psychiatric, social, spiritual, cultural, and ethical assessment and interventions
8. Quality improvement activities are routine, regular, reported, and are shown to influence clinical practice. While the recurrent pregnancy loss care organization leadership is responsible for such programs, there are designated individuals who operate the quality assessment and performance improvement program
9. The clinical practices of recurrent pregnancy loss care programs reflect the integration and dissemination of research and evidence of quality process
10. Quality improvement activities for clinical services are collaborative, interdisciplinary, and focused on meeting the identified needs of women and their families
11. Women, families, health professionals, and the community may provide input for evaluation of the program

Guideline 1.6 The recurrent pregnancy loss management program recognizes the emotional impact on the recurrent pregnancy loss management team of providing care to women with recurrent loss and their families

Principle:

1. Emotional support is available to staff as appropriate
2. Policies guide the support of staff including regular meetings for review and discussion of the impact and processes of providing recurrent pregnancy loss care

Guideline 1.7 Recurrent pregnancy loss management programs should have a relationship with other I/NGOs and other community resources to ensure continuity of the highest-quality recurrent abortion management

Principle:

1. Recurrent pregnancy loss management programs must ensure the continuity of care
2. As appropriate, women and their families are regularly updated and offered referral to other centers as necessary
3. Referring healthcare professionals are regularly informed about the availability and benefits of such action

4. Policies enable timely and effective sharing of information among teams while safeguarding privacy

Guideline 1.8 The physical environment in which care is provided should meet the preferences, needs, and expectations of the woman and her family

Principle:

1. Care is provided in the setting preferred by the woman and her family
2. The setting should address the management needs of the woman and her family

Area 2: Physical Aspects of Management

A protocol describing the details of appropriate and feasible tests and treatments for the management of recurrent pregnancy loss is developed

Guideline 2.1 History taking

History taking is categorized in three phases. Firstly when a couple presents immediately after the loss of pregnancy – third time / more, secondly when the woman presents in the interval period and is planning pregnancy, thirdly when the woman is pregnant.

Principle a:

1. when a couple presents immediately after the loss of pregnancy – third time / more details of the event and investigations are available
2. When the woman presents in the interval period and is planning pregnancy by this time the woman/ couple have recovered from the trauma of loss to some extent
3. When the woman presents in the interval period and is planning pregnancy this gives time for detailed history taking and work-up for planning a new pregnancy
4. When the woman presents in the interval period and is planning pregnancy any coexisting morbidities can be treated
5. When the woman presents in the interval period and is planning pregnancy the couple can be counseled about leading a healthy life-style like avoiding alcohol, cigarette smoking, recreational drug use, maintaining optimal body weight of the woman, stress free life style, regular exercise etc. Prenatal folic acid supplementation can be started
6. The woman is pregnant; the cause of previous abortion should be explored to see if these would have bearing on the present pregnancy. The woman should be treated for coexisting morbidities

Principle b:

1. Complete history of both the couples is essential
2. The focus should be on elaborating the past obstetric events, any treatment for those associated co-morbidities
3. The focus should be on immediate complaints and details of labor/abortion history
4. Any previous treatment should be noted
5. Any psychological complaints/ issues should be explored
6. Discussion regarding their concerns like associated infertility, the psychological trauma, any co-morbidity, intake of drugs is important
7. It is very important to take note of the exact number of previous loss
8. It should be clarified in the history about the number of previous pregnancy loss and gestational age of loss of each pregnancy
9. If records of previous abortion can be obtained, these should be checked
10. If possible, the POC should be sent for Karyotyping

Guideline 2.2 Examination

Principle:

1. Physical examination requires complete general examination to rule out any associated co-morbidities like hypertension, diabetes, anemia , jaundice etc

2. Any evidence of autoimmune or collagen disorders like SLE, hirsuitism, obesity associated with PCOD may be identified during history taking and physical examination

3. Abdominal examination of the woman in woman presenting in the non-pregnant stage include: abdominal examination can suggest any abnormalities like organomegaly or uterine fibroids or ovarian cysts. Pelvic examination. Pelvic examination includes - per speculum examination – any discharge, local lesions like polyps, double cervix etc. Bimanual pelvic examination – to assess uterine size, any fibroids, any ovarian cysts/mass etc

Guideline 2.3 Investigations

Principle:

1. Screening for antiphospholipid syndrome(APS) -Measurement of anti-beta2-glycoprotein I (IgG or IgM) antibodies, anti-cardiolipin (IgG or IgM) antibodies, and lupus anticoagulant, using standard assays (enzyme-linked immunosorbent assay (ELISA)), for diagnosis of antiphospholipid syndrome is essential in women with recurrent pregnancy loss

2. Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage.51

3. Antiphospholipid syndrome is the only immune condition for which pregnancy loss is part of the diagnostic criteria

4. To diagnose APS it is mandatory that the patient should have two positive tests at least six weeks apart for either lupus anticoagulant or anticardiolipin (aCL) antibodies of IgG and/or IgM class present in medium or high titre

5. Screening tests for anti-phospholipid antibodies (both the lupus anticoagulant and anti-cardiolipin antibodies) performed on 2 separate occasions at least 6 weeks apart

6. Discordant results should prompt the performance of a 3rd test

7. Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s).If the test shows chromosomal anomaly then

8. Karyotyping of both couples is done to assess for balanced translocation – Robertsonian translocation. This can be done by peripheral blood smear. If any karyotype abnormalities are identified, the couple should be referred for genetic counseling

9. Ultrasound, and in particular 3D ultrasound, has become an accurate, reproducible, non-invasive, out-patient method for the diagnosis of congenital uterine anomalies toassess uterine size and ovarian morphology like polycystic ovaries

10. HSG/Sonohysterography /Hystroscopy are not needed unless indicated for other conditions. Women with recurrent abortion having uterine septum should undergo hysteroscopic evaluation and resection of the septum if indicated

11. Some tests are not routinely used but used when associated co-morbidities are present - Diabetes mellitus, hyper or hypothyroidism, PCOD, hyperprolcatenemia, Luteal phase defect – diagnosed by endometrial biopsy, tests for inherited thrombophilic disorders: factor V Leiden, prothrombin G20210A mutation, serum homocysteine, and deficiencies of the anticoagulants protein C, protein S, and antithrombin III

Guideline 2. 4 Management

Principle:

1. In reference to RCOG women with recurrent miscarriage who have undergone the above investigations should have all future treatment options evaluated in randomized controlled trials. treatments of unproven benefit should be abandoned, women with persistently positive tests for anti-phospholipid antibodies are offered treatment with low dose aspirin together with low dose heparin during pregnancy (also the subject of on-going research), with karyotypic abnormalities should be seen by a clinical geneticist
2. Cervical circlage requires treatment on time as this is a cause of recurrent pregnancy loss

3. Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should be considered only in women who are likely to benefit
4. Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance
5. Treatment of Antipohospholipid syndrome with aspirin and low dose heparin is recommended
6. Luteal phase deficiency, if confirmed by biopsy, requires progesterone supplementation in the new pregnancy
7. When the woman/ couple present while pregnant with a history of recurrent pregnancy loss, the woman requires extra care
8. Age of the woman is important as advanced age of the woman is one of the risk factors for recurrent pregnancy loss. Age of the woman in years completed should be recorded. The age should be verified if these cases are to be included in any research activities.
9. Associated co-morbidities include – diabetes mellitus, hypertension, thyroid disorders, autoimmune disorders, thrombophilic disorders, celiac disease, endocrine abnormalities like hyperprolactinemia etc.
10. The woman should be advised to delay another pregnancy until cause of recurrent abortion can be investigated
11. This allows time for recuperating and management of other associated illness like diabetes, thyroid disorders, autoimmune diseases etc. There is no evidence is there as how long to delay pregnancy
12. Three -six months should give adequate time for investigations practically

Area 3: Psychological Aspects of Management

Guideline 3.1 Psychological and psychiatric status is assessed and managed based upon the available best evidence

Principle:

1. The multidisciplinary team includes professionals with skills and training in the psychological and psychiatric consequences of recurrent abortion for both woman and her family
2. Evaluation of ongoing assessment of psychological reactions related to the recurrent pregnancy loss is carried out regularly
3. Psychological assessment includes woman understanding of recurrent pregnancy loss management process, capacity of the managing team and the expected outcome
4. Psychiatric, such as severe depression, suicide ideation, anxiety, and delirium, should be treated by a psychiatrist

5. Family is educated and supported to provide safe and appropriate psychological support to the woman
6. Treatment alternatives are clearly documented and communicated and permit the patient and family to make informed choices

Area 4: Social Aspects of Care

Guideline 4.1 A multidisciplinary team evaluates the social needs of women and their families, which is a guideline for the development of management plan

Principle:

1. A multidisciplinary social evaluation is completed and documented to include: family structure and geographic location; relationships; types of communication; existing social and cultural networks; medical decision-making; finances; and caregiver availability
2. A routine meeting is conducted with the woman and her family and the members of the multidisciplinary team to evaluate management plan; determine expectations, and provide emotional and social support
3. The social management plan is formulated from a comprehensive social and cultural assessment and documents values, goals, and preferences as set by the woman and her family

Area 5: Spiritual, and Religious Aspects of Management of Recurrent Abortion

Guideline 5.1 Spiritual and religious dimensions are assessed and addressed

Principle:

1. The multidisciplinary team includes professionals with skill in assessment of and response to the spiritual and religious issues
2. The regular assessment of spiritual and religious concerns is documented. This includes, but is not limited to, assessment of hopes and fears, meaning, purpose, beliefs, guilt, and forgiveness
3. Spiritual/religious needs, and concerns are addressed and documented, and support is offered

Area 6: Cultural Aspects of Management of Recurrent pregnancy loss

Guideline 6.1 The recurrent pregnancy loss management program assesses and attempts to meet the needs of the woman, family, and community in a culturally sensitive manner

Principle:

1. The cultural background, concerns, and needs of the woman and her family are elicited and documented

2. Communication, in all forms, with woman and her family is respectful of their cultural preferences regarding disclosure, truth telling, and decision making
3. Communication should occur in a language and manner that the woman and her family understand

Conclusion:

- **Recurrent pregnancy loss is a social as well as medical problem,hence approach to the patient should be focused on both.**
- **Possible investigation regarding recurrent pregnancy loss should be done based on the causes and individual hospital provision and set up.**
- **As it is time taking with poor outcome ,it is distressing for both the patient and patient party, proper counseling is needed**
- **More research needed in this particular subject as to collect evidence in our country for future management.**

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