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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/16914
DOI URL: http://dx.doi.org/10.21474/IJAR01/16914

RESEARCH ARTICLE

CLINICO-EPIDEMIOLOGICAL PROFILE AND EVIDENCE BASED MANAGEMENT OF RECURRENT MISCARRIAGES IN A TERTIARY CARE CENTRE

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Manuscript Info

Manuscript History
Received: 20 March 2023
Final Accepted: 22 April 2023
Published: May 2023

Abstract

Methodology:An observational prospective study was conducted on 100 patients.
100 patients with recurrent pregnancy losses were studied.
Study was conducted after ethical clearance by ethical committee.
Counselling, Education And Informed Consent
Accurate and realistic information about chances of a successful pregnancy was given depending on the number of losses.
Women were seen in the intercurrent phase between pregnancies and at this visit, a thorough clinical history was recorded and an investigation protocol was followed to exclude known associations with recurrent miscarriage.

Discussion: Early pregnancy loss, also known as miscarriage or Spontaneous abortion, is the loss of a clinical pregnancy before 20 weeks of gestation (18 weeks following conception), or, in cases when gestational age is uncertain, the loss of an embryo or foetus weighing less than 400 gm. Therefore molar, biochemical , and ectopic pregnancies are excluded. It is a rather frequent occurrence, occurring in 15% to 25% of pregnancies and becoming more prevalent as the mother's age increases. In fact, the risk is between 9% and 12% for women under the age of 35, but it rises to 50% for those over the age of 40. Different societies have employed a variety of nomenclatures. Because the causes of each type of miscarriage can vary, the term "miscarriage" can also refer to the loss of an embryo, also known as a "early miscarriage," which occurs before 10 weeks of gestation and "foetal loss," which occurs after 10 weeks. International societies have different definitions of recurrent pregnancy loss (RPL), which has been a subject of much discussion. RPL is defined as three successive pregnancy losses, including nonvisualized ones, by the Royal College of Obstetricians and Gynecologists7 and the European Society for Human Reproduction and Embryology4,6, respectively. The American Society for Reproductive Medicine, however, de fines it as two or more clinical pregnancy losses (verified by ultrasonography or histopathologic study), albeit they don't have to be consecutive. RPL is a significant concern for reproductive health because it affects 2% to 5% of marriages.2,7 Because o f the various definitions and criteria applied, as well as the characteristics of the populations, the incidence of RPL differs significantly between reports. While secondary RPL refers to multiple losses in a woman who

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has already given birth to a child beyond 20 weeks of gestation, primary RPL describes multiple losses in a woman who has never previously given birth to a live baby. Multiple pregnancies lost in between healthy pregnancies are referred to be secondary RPL.

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Introduction:-

Three or more consecutive spontaneous clinically detectable pregnancy losses thatoccurbeforethe20thweekofgestationfromthelastmenstrualperiodareconsideredrecurrentpregnancy losses.[1]

Women who have had three or more consecutive abortions are referred to as "habitualaborters" by LiverpoolnativePercy Malpas[2], who wassupported by Eastman.[3]

0.5–3% of all pregnancies are complicated by recurrent pregnancy loss.[4] Couples findit upsetting, and professionals who care for these patients frequently also find it upsetting. Anumber of different factors play apartintheetiology of these patients. Despiterecentprogress, a sizable percentage isstill unknown. Some of the so-called "unexplained"or"idiopathic" recurrentpregnancylosses willbecategorised as technology develops.

Given how frequently miscarriages occur, it stands to reason that every miscarriagethat is caused by an etiology must occur repeatedly for the term "recurrent pregnancy loss" toapply. This is a tragedy for the couples who waited at least three repeated miscarriages beforefinding areason thatcould havebeen treated and moremiscarriages prevented.

According toaccumulatingdata, the prevalence of different etiological factors iscomparableamongpeoplewhohaveexperiencedtwoormorespontaneousrecurrentpregnancy lossesto thosewho haveexperiencedthree.

Thisisthejustificationbehindstartinganinvestigationforpeoplewhohaveexperienced two or moreconfirmed recurrentmiscarriages.

A number of units in the UK and other countries have adopted this strategy. Someresearchers (Quenby and Farquharson[5], 1993, Stephenson et al[6] 1998, Dubey S et al[7] 2005)includedtwoormoremiscarriagesintheirseries.AccordingtoKuttehetal.(2010)'s"Retrospectiveanalysisof1020womenwithtwoormoreconsecutivespontaneous pregnancy losses," women with varied numbers of miscarriages had similar prevalence ofaberrantoutcomes.[8]

Two previous miscarriages increase the chance of following pregnancy loss by about25% in patients, while three previous abortions increase the risk of a fourth miscarriage byabout33%.[7]
The following are some potential etiological factors: genetic (5%), anatomical (12–16%),endocrine(17–20%),(20–50%)Immunological,(0.5–1.5%)Infections,(5-8%)Thrombophilia, Unknown (30–40%), MaternalSystemicIllness.[9]

It is still difficult to explain the unexplained, which accounts for 30–40% of theetiological causes in recurrent pregnancy loss. To determine the precise cause of recurrentpregnancyloss,aproperproformaorprotocolthatissupportedbybothclinicalandlaboratory datamustbecreated. Henceforth,this study is undertaken.

Material&Methods:-

Study area:
Department of Obstetrics & Gynecology,Studydesign:Observational,prospectivestudyStudy period:1 year, 1/03/21to 28/02/22

Studypopulation–
Thosewithrecurrentpregnancylossesareincluded.

Inclusion Criteria:
Women with history of 2 or more consecutive miscarriagesbefore20weeksofgestation,amongthoseattendingtheoutpatientdepartmentofthehospital.

Exclusion Criteria:
Non-consecutive abortionInduced abortionsGestationabove20weeks

Samplesizeandsampletechnique –
Samplesize– 100cases.

Samplingtechnique–
Randomselection ofpatient.

Justificationofsamplesize
Sample size was calculated by assuming the expected proportion of any particularetiology of recurrent pregnancy loss as 14% as per study by Kutteh William H et al.8 Theotherparametersusedforsamplesizecalculationwere95%confidenceleveland7%precision. The following formula was used for sample size calculation N=(Z^2 P(1-P))/(d^2)

Wheren = Samplesize

Z= Zstatisticforalevelof confidence= 1.96

P = Expected prevalence of proportion(If the expected prevalence is 20%, then P¬ = 0.14),and D= Precision (If theprecisionis5%, then d=0.07).

N=(〖1.96〗^20.14(0.86))/(〖0.07〗^2)

Therequiredsamplesizeaspertheabove-mentionedformulawas95subjects.Toaccountfor 5% non-participation rate, another 5 subjectswere included inthe study.Hence therequired sample size for the study was 100. Keeping in mind the given duration of the studyand concerned patient flow in this setup, it was decided to recruit all available subjectssequentially tillthesamplesizeis reached.

Data collection technique and toolsDatacollectiontechnique
Primary data – History and clinical examination, laboratory dataSecondarydata –Systematicreviews andresearch synthesis.

Tools
Directobservations,interviews,protocols,tests,examinationofrecords,andcollectionsofwriting samples.

Methodology:-

Anobservationalprospectivestudywas conductedon100patients.100 patients with recurrentpregnancy losses werestudied.

Studywasconductedafterethicalclearancebyethicalcommittee.Counselling, Education And Informed Consent

Accurateandrealisticinformationaboutchancesofasuccessfulpregnancywasgivendepending on thenumber oflosses.

Women were seen in the intercurrent phase between pregnancies and at this visit, a thoroughclinical history was recorded and an investigation protocol was followed to exclude knownassociations with recurrentmiscarriage.

Investigations
All patients having history of recurrent abortion before 20 weeks of gestational period wereinvestigated on OPD basis, to find out aetiological factors of recurrent pregnancy loss. Theinvestigations included:-

Complete blood countPlateletcount
Urineroutine:
Blood Sugar-F , PP / OGCT /OGTTUltraTSH

Serum ProlactinAPLA
Anticardiolipin antibodies:- IgM,IgGLupus anticoagulant:-
Antinuclear antibodiesSerumHomocysteinelevel
Pelvic UltrasoundKaryotyping ofpartnersDiagnosticHysteroscopy

Insomecases,patientsrequiredadditionalinvestigationsonthebasisoftheirhistoryandclinicalfindingsso asto establish thecausefor miscarriages

TheAdditionalInvestigationsOrEvaluationsWereThrombophiliascreening
Protein CProtein SAntithrombin IIIFactorVLeiden
Tissue plasminogen activator (TPA)DiagnosticLaparohysteroscopy
Atthefollowupvisit,resultsandplanforthemanagementofsubsequentpregnancyworediscussed.
Allwomen wereadvised totakepreconceptionalfolicacid.

In a subsequent pregnancy, women were seen after a week of a missed period. An ultrasoundwas performed to note the presence of an intrauterine sac and fetal cardiac activity. Weeklyfollow up visitsand ultrasound was performedtillthey reached 12-14 weeks.

Treatment of thyroid disorders and diabetes if detected was startedprior to conception andcontinuedthroughout.

Correctableuterineanomaliesdiagnosedweresubjectedtooperativehysteroscopy.

Data was entered inchronological order including demographic details, relevant past history(medical,surgical),obstetrichistory,resultsofinvestigation,detailsandoutcomeofsubsequentpregnancy.

In case of a subsequent miscarriage, the gestation atmiscarriage and details of whethercardiacactivity wasever identified wererecorded.

If miscarriage occurred before fetal cardiac activity was identified, the pregnancy loss wasdefined as an embryonic loss. If it occurred after fetal cardiac activity was identified, thepregnancy losswasdefined asafetalloss.

Maternal age has been shown as an independent factor in predicting pregnancy outcome. Subgroup analysis was therefore undertaken for women aged below 35 years and above 35 years.This age was chosen as it is the age at which the risk of aneuploidyin pregnancy risessignificantly.

Clinicalevaluationwasdoneasperfindingsofcase history,proformaandstatisticallyanalysed.

Dataanalysis:
Datawascollectedinpredesignedandpretestedproformawithapplicationofsuitabledescriptiveand inferentialstatisticsaccordingly.

Datawas analyzedusingSPSS version23.Descriptivestatisticsweredone.Appropriate test of statistical significance was applied wherever necessary.A p value< 0.05 isconsidered significant.

ObservationandResults:-

Datawas analyzedusingSPSS version23.Descriptivestatistics weredone

Table2:- Distributionaccordingto agegroup.

AgeGroup	Frequency	Percent
<20Years	1	1.0
21-25Years	8	8.0
26-30Years	48	48.0
31-35Years	38	38.0
>35Years	5	5.0
Total	100	100.0

Asperagegroup,1patientbelongedto<20years,8(8%)to21-25years,48(48%)to26-30years, 38 (38%) to 31-35 yearsand 5 (5%) to >35 years.

Figure1:- Bardiagramshowingagegroups.

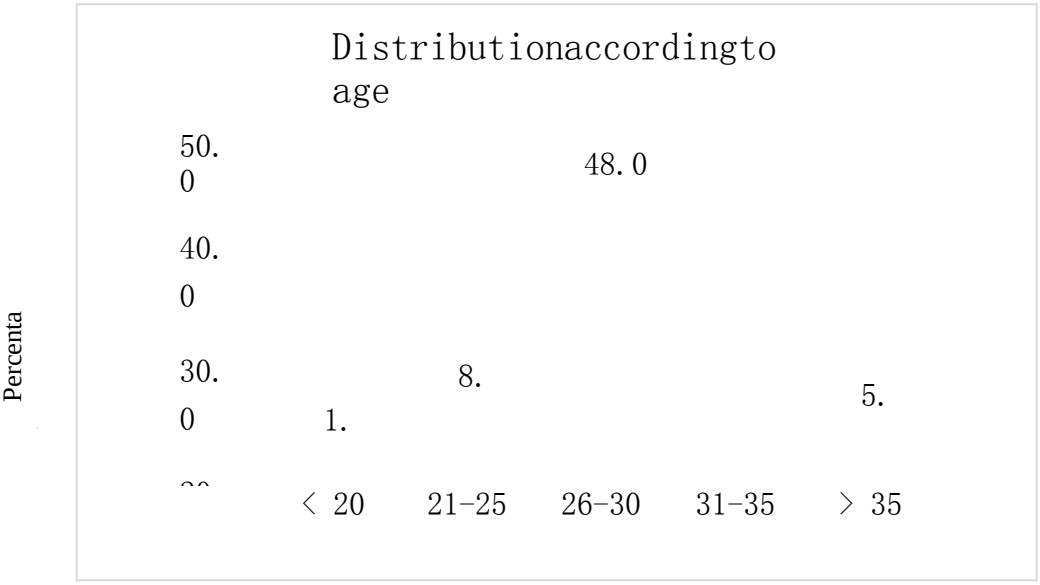


Table 3:- Distributionaccordingtoeducation.

Education	N	%
Illiterate	26	26.0
Primary	35	35.0
Secondary	36	36.0
Graduate	3	3.0
Total	100	100.0

In this study participants, 26 (26%) were illiterate. Of the remaining, 35 (35%) completedprimaryeducation,36(36%)completedsecondaryeducationand3(3%)completedgraduation.

Figure2:-Piediagramshowingeducation.

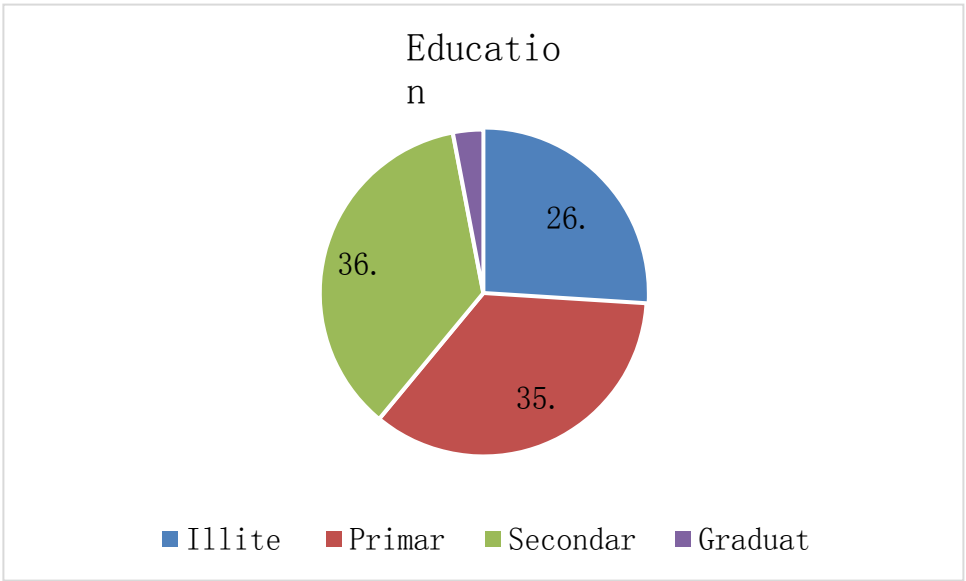


Table4:- Distribution accordingtoSocioeconomicstatus.

Socioeconomic class	Frequency	Percent
Class2	2	2.0
Class3	24	24.0
Class4	35	35.0
Class5	39	39.0
Total	100	100.0

Amongthestudysubjects,aspersocio-economicstatus,2(2%)belongedtoclass2,24(24%)belonged toclass 3, 35 (35%)belongedto class 4 and39 (39%) belonged to class 5

Figure 3:- Bardiagram showing socio-economicstatus.

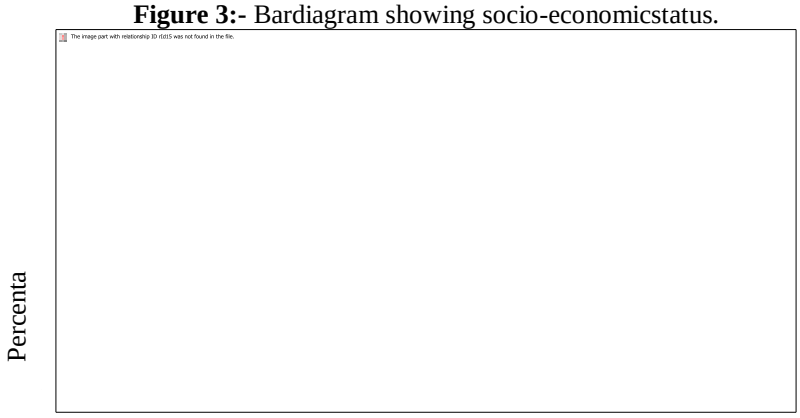


Table5:-Obstetricscore.

Obstetricscore	Frequency	Percent
G10P9L1	1	1.0
G3A2	51	51.0
G3P1L0A2	5	5.0
G3P2L0	6	6.0
G4A3	13	13.0
G4P1L0A3	1	1.0
G4P1L1A2	10	10.0
G5A4	3	3.0
G5P1L1A3	8	8.0
G6P1L1A4	1	1.0
G7A6	1	1.0
Total	100	100.0

Majorityobstetricstatus wereG3A2 (51%)followedbyG4A3 (13%)andG4P1L1A2(10%).

Figure4:- Bardiagramshowingobstetricscore.

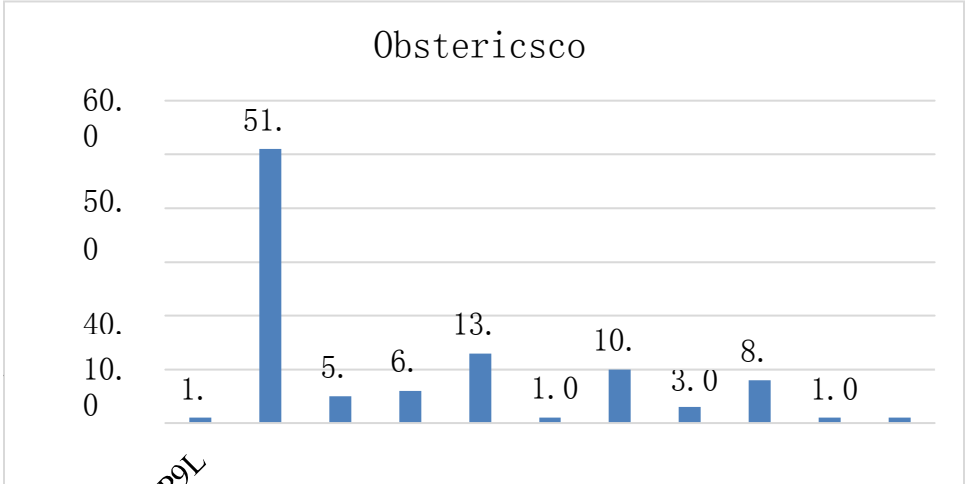


Table 6:- Hormonaletiology.

Hormonal abnormality	Frequency	Percent
Diabetesmellitus	3	3.0
Hashimoto Thyroiditis	1	1.0
Hyperthyroid	6	6.0
HypoThyroid	17	17.0
Hyperprolactinemia	6	6.0

As per hormonal etiology, 3 (3%) were having diabetes mellitus, 1 (1%) had Hashimotothyroiditis, 6 (6%) were hyperprolactinemic, 6 (6%) were hyperthyroidic and 17 (17%) werehypothyroidic

Figure5:-Bar chartshowingHormonal etiology.

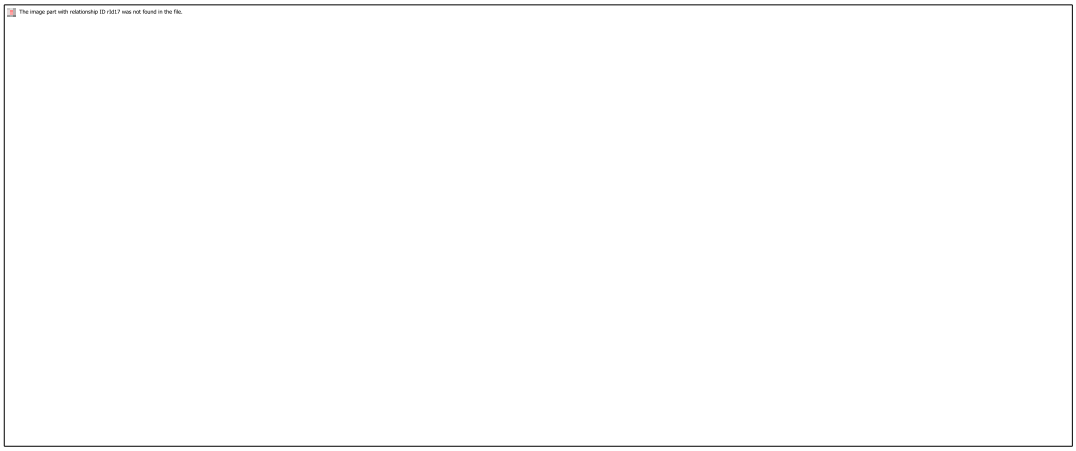


Table7:-Anatomicaletiology.

Anatomical	Frequency	Percent
Cervical Incompetence	6	6.0
Submucous	1	1.0

Fibroid		
Septate Uterus	1	1.0
Total	100	100.0

Asperanatomicaletiology,6(6%)hadcervicalincompetence,1(1%)hadsubmucousfibroid,1 (1%) had septateuterus.

Figure 6:- Bar chartshowinganatomical etiology.

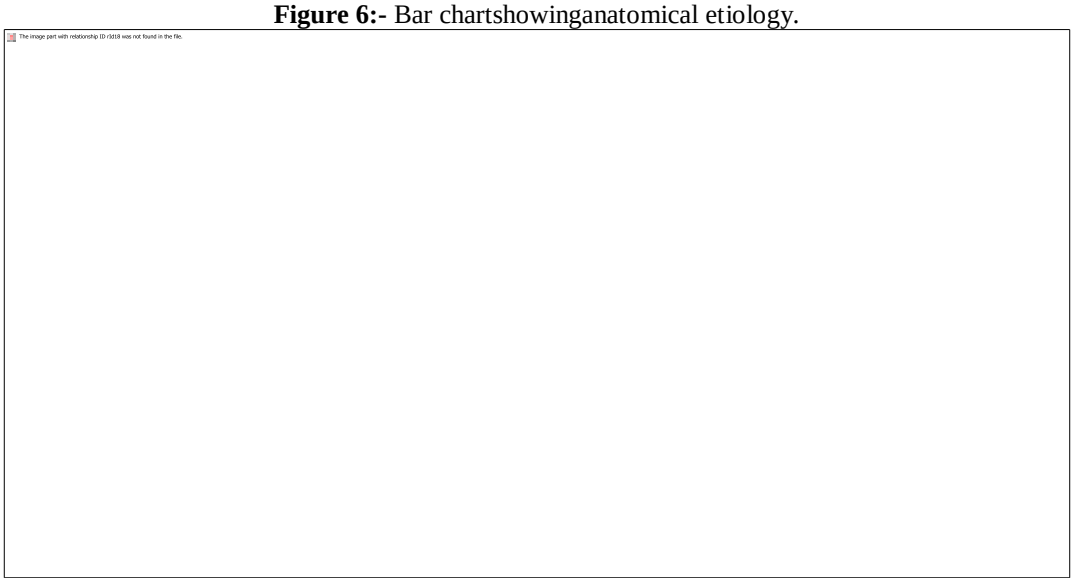


Table 8:- Immunological.

Immunological	Frequency	Percent
APLA +	3	3.0
Normal	97	97.0
Total	100	100.0

Asperimmunologicaletiology,3(3%)hadAPLA+status

Figure7:-Piechartshowing immunologicaletiology.

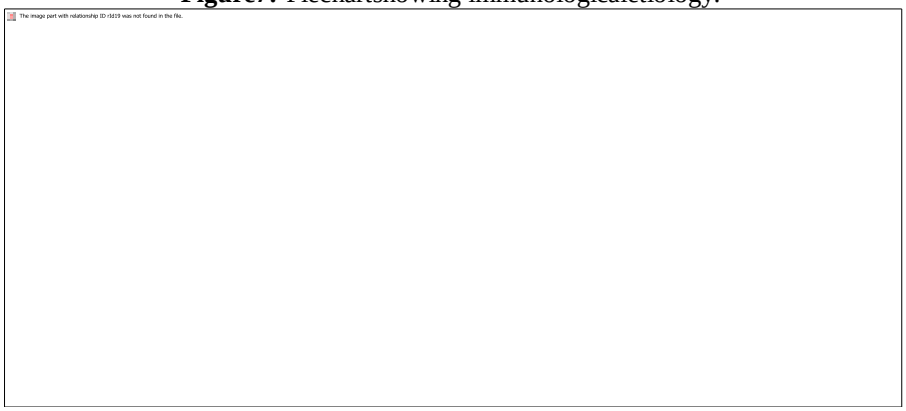


Table9:- Genetic.

Genetic	Frequency	Percent
Chromosomal Abnormality	3	3.0
Unknown	97	97.0

Total	100	100.0

3 (3%)hadchromosomalabnormality.

Figure8:-Piechartshowinggenetic etiology.

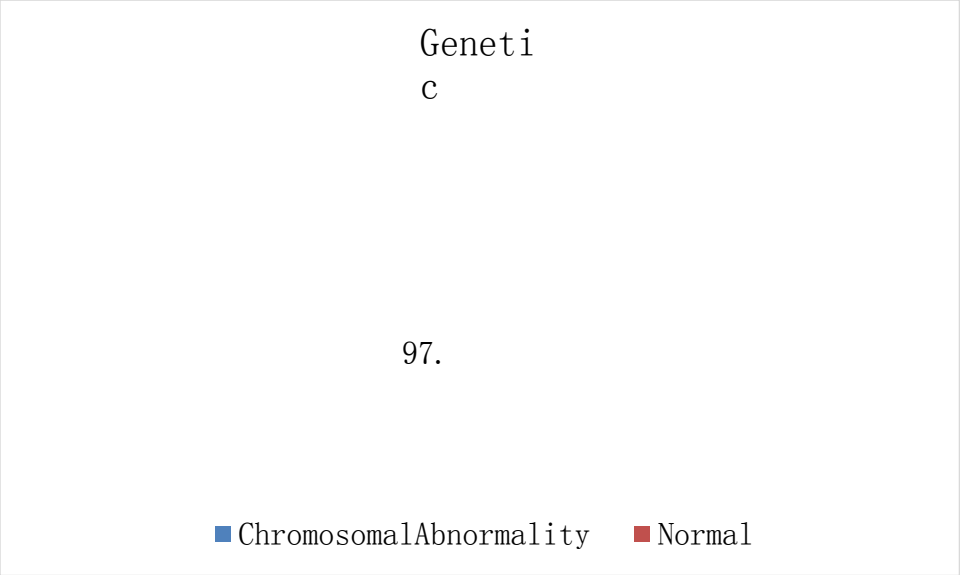


Table10:-Others.

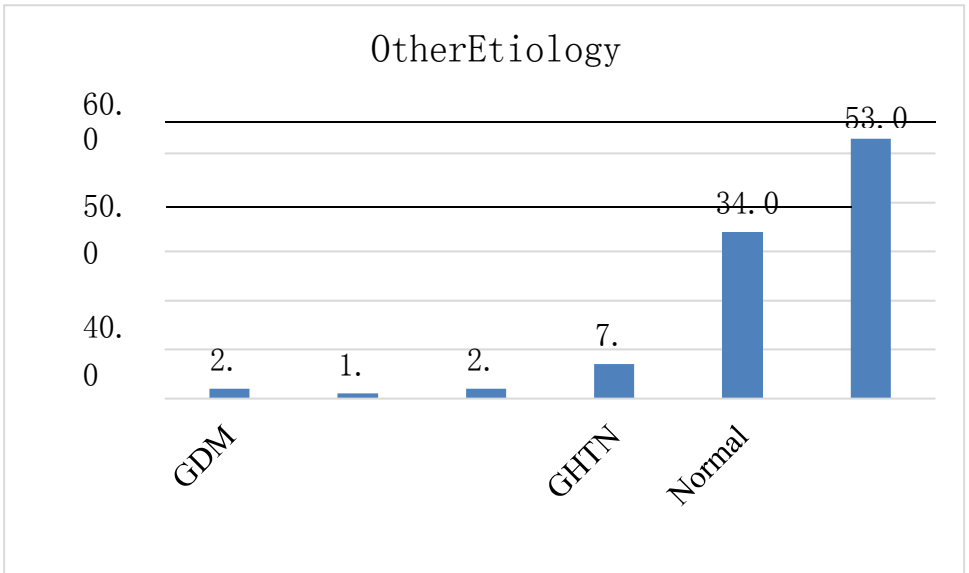
Others	Frequency	Percent
GDM	2	2.0
GDM(I)	1	1.0
GDM, HTN	2	2.0
HTN	8	8.0
Normal	34	34.0
Unknown	53	53.0
Total	100	100.0

2 (2%) had GDM, 1 (1%) had GDM (I), 2 (2%) hadGDM &HTN, 8 (8%) hadHTN.

34(34%)werenormal.

53(53%)hadunknownetiologies.

Figure9:-Barchartshowingotheretiologies.



Discussion:-

Earlypregnancyloss,alsoknownasmiscarriageorspontaneousabortion,isthelossofaclinical pregnancybefore 20weeksofgestation(18weeksfollowingconception),or,incases when gestational age is uncertain, the loss of an embryo or foetus weighing less than 400 g.1Therefore, molar, biochemical, and ectopic pregnancies are excluded.2 It is a rather frequentoccurrence,occurringin 15%–25% ofpregnancies and becomingmoreprevalent as themother's age increases.2,3 In fact, the risk is between 9% and 12% for women under the ageof 35, but it rises to 50% for those over the age of 40.3 Different societies have employed avariety of nomenclatures.4,5 Because the causes of each type of miscarriage can vary, theterm"miscarriage"canalsorefertothelossofanembryo,alsoknownasa"earlymiscarriage," which occurs before 10 weeks of gestation and "foetal loss," which occurs after10 weeks.4,5 International societies have different definitions of recurrent pregnancy loss(RPL), which has been a subject of much discussion. RPL is defined as three successivepregnancy losses, including nonvisualized ones, by the Royal College of Obstetricians andGynecologists7 andthe European Societyfor Human ReproductionandEmbryology4,6,respectively. The American Society for Reproductive Medicine, however, defines it as two ormore clinical pregnancy losses (verified by ultrasonography or histopathologic study), albeitthey don'thaveto beconsecutive.

RPLisasignificantconcernforreproductivehealthbecauseitaffects2%to5%ofmarriages.2,7Becauseofthevariousdefinitionsandcriteriaapplied,aswellasthecharacteristics of the populations, the incidence of RPL differs significantly between reports.While secondary RPL refers to multiple losses in a woman who has already given birth to achild beyond 20 weeks of gestation, primary RPL describes multiple losses in a woman whohas never previously given birth to a live baby. Multiple pregnancies lost in between healthypregnancies arereferred to besecondary RPL.4,5

Age:

Asperagegroup,1patientbelongedto<20years,8(8%)to21-25years,48(48%)to26-30years,38(38%)to31-35yearsand5(5%)to>35years.AgeofthemotherisprobablyariskfactorforRPLaswellassporadicmiscarriage.194Meioticmistakesinoocytedevelopmentthatresultinincreasedembryonicaneuploidyaremorecommoninwomenover35(referredtoas"advancedmaternalage"[AMA]).94Whencomparedtowomenover40,thereportedmiscarriagerateforthoseunder35is14%,whileitis40%forthoseover40.195Giventhis,one would anticipate that the RPL rate in women over 40 would be more than 20 times higherthanthatinwomenunder35.TheactualprevalenceofRPLinwomenover35isunknown,though.Accordingtoastudyfrom1996,awoman'sriskofmiscarriageriseswithage.Awoman finds it harder both to become pregnant and to maintain her pregnancy.196

HormonalCauses:

As per hormonal etiology, 3 (3%) were having diabetes mellitus, 1 (1%) had Hashimotothyroiditis, 6 (6%) were hyperprolactinemic, 6 (6%) were hyperthyroidic and 17 (17%) werehypothyroidic. Recurrent miscarriages are significantly influenced by severe maternal illnessconditions. The most common screenings for women are for diabetes, thyroid issues, andhyperprolactinemia. Miscarriage has been linked to systemic maternal endocrine conditionssuch as diabetes mellitus and thyroid illness. Endometrial development can be impacted byendocrinevariables,andadequateendometrialdevelopmentisnecessaryforsuccessfulimplantationandthecreationofthefeto-maternalunit.Accordingtothecurrentstudy,endocrine variables were thought to be responsible for about 5% of all miscarriages, which issimilarto thefindings of thestudy doneby Arredondoetal(8%).209

Diabetes:

In the current study, the likelihood that diabetes is an etiological factor is 3%. 3 of the 100cases in the current investigation had diabetes. Before becoming pregnant, 1 patient wasreceivinginsulintreatmentandwasundergoodcontrol.Thepatienthadacaesareandelivery.

Thus, the likelihood of miscarriageisreduced ifdiabetesisunder good control. Thesefindings wereconsistent withstudy done by Abalovichet al210,which discoveredthatthyroid dysfunction or well-controlled diabetes did not increase the incidence of recurrentmiscarriage. Similar to this, a study by Mills JL et al211 discovered that diabetes mellitus,while under good care, does not increase the incidence of recurrent miscarriage. Women withdiabetes who have high HbA1c levels in the firsttrimester are at risk of miscarriage andfoetal deformity, according to Hanson U et al.212 In two earlier investigations, poor glucosetolerance was more common in women who experienced recurrent miscarriages (17.0% byHughes etal213;22.8% byTulppalaetal214).

Thyroid:
In our study, out of 100 instances, 17 cases (17%) had hypothyroidism and were giventhyroxine to treat it. The dosage was regularly monitored and modified based on the levels offree T4 and TSH. 6 (35.2%) of the instances resulted in a typical vaginal delivery, while 9(52.9%)continuetobepregnantafter28weeks.Thisstudyiscomparabletotheoneconducted by Rao V et al215, who discovered that hypothyroidism was present in 4.12% ofwomen who had previously lost pregnancies and that treating hypothyroidism could improvethe chances of future pregnancy success for such couples. According to Kutteh et al216,thyroid antibodies and repeatedmiscarriages are related.They proposedthat this might justbe a symptom of an all-encompassing autoimmune illness. According to a case-control studydone by Esplin MS et al217, women who have recurrent miscarriage are not more likely tohavecirculatingthyroidantibodiesthancontrols.Ina1990sstudy,itwasfoundthateuthyroidwomenwhopresentedwiththyroidantibodiesexperienceda2-to4-foldincreasein miscarriage rates.218 A 1996 study by Singh et al219 provided evidence in favour of this.Theexistenceofthyroidantibodiesineuthyroidwomenwithahistoryofrecurrent miscarriage,however,hasnotbeendemonstratedtohaveanimpactonthesuccessofsubsequent pregnancies, according to a prospective research done by Rushworth et al.220HYPERPROLACTINEMIA:

Contradictoryinformationregardinghyperprolactinemia'sroleinrecurrentpregnancylossmakes itunclear whether itservesas arisk factor forthecondition.52,74

In the current study, 6 individuals (6%) out of 100 cases had hyperprolactinemic symptoms.Theyhadcabergolinetreatment.Outof6patients,3(50%)hadsuccessfulfull-termdeliveries,1(16.66%)wasstillpregnantat28weeks,and2(33.3%)instanceswereintercurrent.Agreaterrateofsuccessful pregnancyoutcomewasobservedinwomenwhoreceivedtreatmentforhyperprolactinemiainarandomisedcontroltrialconductedbyHiraharaetal53whichincluded64womenwithhyperprolactinemiaandrecurrentmiscarriages.Prolactinlevels intheblood shouldbeadequatetomaintainearly pregnancy.

AnatomicalCauses:
Asperanatomicaletiology,6(6%)hadcervical incompetence,1(1%)hadsubmucousfibroid,1 (1%) had septateuterus.

Obstetric complications have long been linked to architecturally abnormal uteri. The mostprevalenttypesofreproductivesystemmalformationsarecongenitaluterinedeformitiesbroughton by mullerian fusion disorders.

In our study, 1 instance (1%) out of 100 cases had an intrauterine septum and experiencedrepeatedspontaneousmiscarriages.Aseptoplastywasperformedinlightoftheuterineabnormality.Sheis currentlycarrying her pregnancythrough 28 weeks of gestation.

In their article on the clinical consequences of uterine malformations and the outcomes ofhysteroscopic treatment, Grimbizis GF et al16 noted that the prevalence of uterine anomaliesinthepopulationofwomenwhoexperiencerecurrentmiscarriagesrangedbetween1.8%and 37.6%. This variation is due to the fact that different diagnostic methods and criteria havebeen employed, as well as the fact that studies have included women who had experiencedtwo, three, or more losses at both early and late stages of pregnancy. Similar findings werefound in the study by Ventolini G et al199, which indicates that 8.7% of individuals whoexperienced three or more unexplained miscarriages had septated uteri. In a survey of allpregnancies in a population with congenital abnormalities conducted by Raga F et al200, itwas discovered that women with septate uteri had a 25.5% early miscarriage rate (13 weeks)anda6.2%latemiscarriageincidence(14–22weeks).Thissuggeststhatauterineseptummay influence both early and later embryo development following implantation, leading tomiscarriage in the first and second trimesters as well as early labour. According to Salim R etal201, 85% of hysteroscopicresectionsaresuccessful.

Out of 100 cases in the current study, 1 (1%) had submucous fibroids together with recurrentmiscarriage. A hysteroscopic myomectomy was done. She is still pregnant after 28 weeks ofgestation. 4.3% of patients had submucous myomas with a history of repeated miscarriages,according to Ventolini G et al.199 Although they are linked to mid-trimester losses, fibroidsmay also be to blame for early pregnancy losses if they are causing the endometrial cavity tosag. The likelihood that submucous intracavitary fibroids will prevent an early pregnancyfromprogressingsuccessfullyisthehighest.Thepreferredmethodishysteroscopicmyomectomy,and accordingto a numberof retrospective and cohort studies, removingsubmucous fibroids lowers the miscarriage rate. Overdiagnosis

of cervical weakness as acause of midtrimestermiscarriage is common. Currently,there is no reliable objective testthat can detect cervical weakening in women who are not pregnant. The diagnosis is typicallybased on a history of a late miscarriage that was preceded by an unnoticed cervical dilation orspontaneous membranerupture.

In the current study,6 out of 100 cases (6%) between 14 and16 weeks ofgestation hadashort cervix as determined by USG and clinical examination. They all successfully deliveredat term after undergoing cervical encerclage using the McDonald's procedure, indicating thatthis may be one of the etiological explanations for their repeated pregnancy loss. Theseoutcomes were comparable to those of the MRC/RCOG elective cerclage trial, which showeda modest reduction in preterm birth and the delivery of babies with very low birth weights.However, the benefit was more pronounced in women who had three or more preterm birthsor miscarriages in the second trimester. However, the perinatal survival did not significantlyimprove.202 After ultrasound-indicated cervical encerclage, two randomised controlled trialswere unable to show any meaningful improvement in perinatal survival.203,204 However, itwas found in the current study that cervical encerclage, when performed in instances withshort cervixes, which may have been the cause of recurrent loss, contributed to enhancepregnancy outcomes.

ImmunologicalCauses:
Asperimmunologicaletiology,3(3%)hadAPLA+status

The unique autoimmune condition known as APS has become a significant factor in thedevelopment of recurrent miscarriages. It is now a widely acknowledged cause of recurrentmiscarriageandislikelythemostcurableone.Antiphospholipidantibodiesandpoorpregnancyoutcomesorvasculart hrombosisarebothassociatedwithprimaryantiphospholipid antibody syndrome (APS). The suppression of trophoblastic activity anddifferentiation as well as, in later pregnancy, thrombosis of the uteroplacental vasculature aretwo mechanisms by which APLAcauses pregnancymorbidity.

3 out of 100 cases (3%) in the current investigation had an APLA positive diagnosis. 1 casetestedpositiveforLA,1instancetestedpositiveforACA,1casetestedpositiveforboth ACA and LA. Low dose aspirin and low molecular weight heparin are used to treat pregnantwomen who are currently carrying a child. In the current study, 66% (2) of the patients werestill pregnant after 28 weeks, and 33 % (1) patients gave birth to healthy babies at term. Ourfindings were nearly comparable to study by Rai R et al, which revealed that 15% of thesewomen had antiphospholipid syndrome.205 According to another study by Rai RS et al,women who suffer from recurrent miscarriage linked to APLA and are treated with low doseaspirin alone have a 40% live birth rate; this rate rises to 70% when they get low dose aspirincombined with low dose heparin.122 According to a meta analysis by Empson M et al37,treatment with low dosage heparin and low dose aspirin dramatically reduced pregnancylossesby54%incomparisontoaspirinaloneinwomenwithahistoryofrecurrentmiscarriage linked to APLA. According to a recent randomised controlled trial, aspirin alonehad a high success rate and the addition of heparin did not significantly increase the live birthrate. However, this study also included women with low APLA titres, some of whom wererandomly assigned at 12 weeks' gestation, by which time the majority of APLA-relatedpregnancy losses would have already taken place.206 According to two small randomisedcontrolled trials, giving steroid medication topregnant women who experience recurrentmiscarriage linked to APLA did not increase the live birth rate in comparison to giving themaspirin or aspirin with heparin. Significant maternal and foetal morbidity is linked to steroidtherapy.207,208

GeneticCauses:
3(3%)hadchromosomalabnormality.

Adefectiveembryothatisnotcompatiblewithlife,suchasonewithchromosomalabnormalitiesor structural deformities, may be the cause of recurrent pregnancy losses.Infertility doctors agree that specific chromosomal abnormalities are to blame for recurrentpregnancylosses.Thankfully,theseanomaliesarenotcommon.Boththematernaland paternalchromosomesmayincludethem.Intheirstudy,OgasawaraMetal89discoveredthattheprevalenceofchromosomalab errationreducesandthelikelihoodofrecurrentmaternalcausesincreases asthenumber ofmiscarriages rises.

Chromosomal abnormalities were shown to be the cause of 3 (3%) of the 100 instances in thecurrent investigation that resulted in recurrent miscarriages. Previous studies by Werner M etal90, Stephenson MD et al93, Franssen MT et al100, Munne S et al155, Dahdouh EMetal163 and Gajjar K et al175 had confirmed similar results. However, a 1998 study analysisfound that 2.5% of 160 women who had experienced repeated miscarriages had

aberrantkaryotypes.Intheircytogeneticexaminationsofcoupleswhohadrepeatedlylostpregnancies,DeBraekeleerMetal91 foundthatbalancedreciprocalorRobertsoniantranslocations werethemostprevalentkind ofparentalchromosomalabnormality.

3 (3%) of the patients in the current study had balanced translocation in just one partner.These 3 patients are now all attempting pregnancy. This is consistent with research by VanDyke DL et al197 and Jacobs PA et al198, which suggests that 5% of recurrent miscarriageshave balanced translocations. Preconception genetic counsellingwas providedtoall 3ofthesepatients.

Other Causes:
3 (3%) had GDM, 2 (2%) had GDM & GHTN, 8 (8%) had GHTN. 53 (53%) had unknownetiologies.

The likelihood of a successful pregnancy dependson both the underlying cause and howmanymiscarriageshavealreadyoccurred.Themanagementoftheseladiesincludedetermining the cause and administering the appropriate therapy. About half of the cases stillhave no known cause. In this investigation, it was discovered that the majority of cases ofrecurrentmiscarriagehadnoknownreason.In53of100cases(53%),therewasnounderlyingfactorthatcouldaccountforthew omen'srepeatedmiscarriages.30ofthe53 instances were pregnant throughout the time of the study, and 23 of the cases are currently inthe intercurrent phase. 15 (50%) of the 30 pregnant women are still carrying their babies at 28weeks of gestation, 14 (46.66%) had healthy babies at term, and one (3.33%) suffered asecond miscarriageat10 weeks.

Despite all investigations, there are still many recurring miscarriage cases that go unsolved.Theseladiesneedtobereassuredthatadequatesupportivecarealonecanresultinasuccessful pregnancy in 75% of cases.87 Although the mechanism is unknown, data frommultiple non-randomized studies have suggested that visiting a specialised early pregnancyclinic has a positive effect. According to this information, empirical treatment should not beused on women who experience unexplained recurrent miscarriage and should instead beavoided.221Asa result,the patient shouldreceive encouragement at eachstage oftheevaluation. It is crucial to highlight to the patient that there is no concrete proof that anythingtheydidordidnotdocausedtheloss duetothementalpainbroughtonbyrepeatedspontaneous miscarriage. Pointing them that a better lifestyle free of smoke, alcohol,
illegalsubstances,andexcessivestressmayconsiderablyincreasethecouple'schancesofconceivingsuccessfully.Itisimporta nttohighlightlifestyle adjustmentandstress reduction.

Conclusion:-

1. The present study was conducted to know the different etiological factors susceptible forrecurrent miscarriages, clinical presentation of different cases and implementation of specifictreatmentto thefactordiagnosedin atertiary carecenter.
2. As per age group, 1 patient belonged to <20 years, 8 (8%) to 21-25 years, 48 (48%) to 26-30years,38(38%)to31-35yearsand5(5%)to>35years.Themother'sagemaybearisk factor for both RPL and random miscarriage. Women over 35 are more likely to have meioticerrors in oocytedevelopmentthatleadtomoreembryonicaneuploidy.
3. As per hormonal etiology, 3 (3%) were having diabetes mellitus, 1 (1%) had Hashimotothyroiditis, 6 (6%) were hyperprolactinemic, 6 (6%) were hyperthyroidic and 17 (17%) werehypothyroidic.Endometrialdevelopmentcanbeaffectedbyhormones,andahealthyendometriumis neededforimplantationandtheformationofthefetus-motherunit.
4. In the current study, there is a 3% chance that diabetes is one of the causes. Three of the 100people being looked into in this study had diabetes. Before getting pregnant, one of thepatients was taking insulin and was doing well. The woman gave birth through a caesareansection.So,thereis lesschanceof amiscarriageifdiabetesis wellmanaged.
5. 17cases(17%)hadhypothyroidism,whichwastreatedwiththyroxine.Thedosewaschecked often and changed based on how much free T4 and TSH was in the blood. In 6(35.2%) of the cases, the baby was born through the birth canal, while 9 (52.9%) of thewomenwerestillpregnantafter 28 weeks.
6. In the current study, 6 out of 100 people (6%) had symptoms of hyperprolactinemia. Theywere given cabergoline. Three of the six patients (50%) had full-term deliveries that wentwell, one (16.66%) was still pregnant at 28 weeks,and two (33.3%) cases happened morethanonce.
7. Asperanatomical etiology,6(6%)hadcervicalincompetence,1(1%)hadsubmucousfibroid,1 (1%) had septateuterus.

8. In our study, 1 instance (1%) out of 100 cases had an intrauterine septum and experiencedrepeatedspontaneousmiscarriages.Aseptoplastywasperformedinlightoftheuterineabnormality.Sheis currentlycarryingherpregnancythrough 28weeks ofgestation.
9. Out of 100 cases in the current study, 1 (1%) had submucous fibroids together with recurrentmiscarriage. A hysteroscopic myomectomy was done. She is still pregnant after 28 weeks ofgestation.
10. In the current study, 6 out of 100 cases (6%) between 14 and 16 weeks of gestation had ashort cervix as determined by USG and clinical examination. They all successfully deliveredat term after undergoing cervical encerclage using the McDonald's procedure, indicating thatthis maybeoneof theetiologicalexplanationsfortheir repeatedpregnancyloss.
11. 3 out of 100 cases (3%) in the current investigation had an APLA positive diagnosis. 1 casetested positive for LA, 1 instancetested positive for ACA,1 case tested positive for bothACA and LA. Low dose aspirin and low molecular weight heparin are used to treat pregnantwomen who are currently carrying a child. In the current study, 66% (2) of the patients werestillpregnantafter28weeks,and33%(1)patients gavebirthtohealthybabies atterm.
12. Chromosomal abnormalities were shown to be the cause of 3 (3%) of the 100 instances in thecurrent investigation that resulted in recurrent miscarriages. 3 (3%) of the patients in thecurrent study had balanced translocation in just one partner. These 3 patients are now allattemptingpregnancy.
13. In this investigation, it was discovered that the majority of cases of recurrent miscarriage hadno known reason. In 53 of 100 cases(53%), there wasno underlying factor that couldaccountforthewomen'srepeatedmiscarriages.30ofthe53instanceswerepregnantthroughoutthetimeofthestudy, and23ofthecasesarecurrentlyintheintercurrentphase.15 (50%) of the 30 pregnant women are still carrying their babies at 28 weeks of gestation, 14(46.66%) had healthy babies at term, and one (3.33%) suffered a second miscarriage at 10weeks.
14. It is important to tell the patient that there is no proof that anything they did or didn't docausedtheloss.Thisisbecauserepeatedspontaneousmiscarriagescancausealotofmental pain. It could be informed that their chances of getting pregnant are much higher if they quitsmoking, drinking, using illegal drugs, and havingtoo much stress. It's importantto talkaboutchangingtheir lifestyleand getting rid of stress.

StrengthsAndLimitations:

1. Data used in this study are population-based and include information from primary observerdataandlaboratory investigations.
2. Dataareupdatedoften,andfollow-uploss is absent.

3. Afurtherdrawbackwasthetinysamplesize.Highercommunitylevelresearchandmulticentricinvestigations with larger samplesizes might be required tocounteract thisaberration.

Recommendations:-

1. Thereisaneedtoconductfurtherlarge-scalestudiesonthesubjecttoenhanceourunderstandingofthevarious unexplainedfactorsassociatedwith recurrentpregnancylosses
2. There is a need to establish continuous surveillance system at each tertiary center to monitortheirchanging trends.

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