Recurrent Pregnancy Loss

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To lose a pregnancy repeatedly, time after time is a very frustrating experience for the patient, her relatives and of course her Obstetrician.

Recurrent Pregnancy Loss is defined as the spontaneous termination of a pregnancy before 20 weeks of gestation with the fetal weight less than 500gms occuring atleast 3 times in succession. This is a relatively uncommon condition with an estimated risk of about 0.4 to 1%.

Recidive abortions, on the other hand is an occurance of two consecutive spontaneous pregnancy wastages before 20 weeks of gestation, with at least 1 fetus weighing less than 500gms.

Distinct identification of the number of spontaneous abortions is important, since it indicates the risk of losing the next pregnancy.

Risk of Recurrent Early Pregnancy Loss

	No. of Prior Losses	% Risk of Loss in next pregnancy
At least one live born infant	0	12%
	1	24%
	2	26%
	3	32%
	4	26%
No live born infant	2 or more	40-45%

The chance of a live birth after three abortions is 55 to 60%, while one previous normal pregnancy increases the incidence to 70%.

From a clinical point of view, the patients are extremely distressed with this apparently "recurring" phenomenon and seek adequate explanation as well as preventive treatment for future pregnancies.

Habitual aborters have been classified as primary when there is no evidence of auto-antibodies or blocking antibodies and secondary when there is no evidence of auto-antibodies but antibodies to paternal antigens are present.

Though, many causes of recurrent abortions have been postulated the cause of individual abortions in a couple with recurrent pregnancy loss is not always the same, and often factors may co-exist. However, in about 40-50% of cases no etiological factor can be identified. Potential causes have been classified into two groups. 1. Possible-where the association between the cause & the result has scientific validity but final proof is still lacking. 2. Doubtful, where data suggests a loose association.

Possible Causes:

1. Genetic - About 50% to 60% of spontaneous first trimester abortions have an abnormal karyotype as compared with a 7.3% incidence in planned abortions. 30% of second trimester abortions and 3% of still births have abnormal chromosomes.

   The most common abnormalities are:
   Trisomies 52%, polyploidy 26%, X-monozomy 15% and the rest - double trisomies, mosaicism and translocations accounting for 7%. If the first pregnancy has a normal karyotype, but ends in a spontaneous abortion, the subsequent pregnancy will be chromosomally abnormal in about 50%. However, if the first abortus is chromosomally abnormal, the next pregnancy has an 80% chance of karyotypic abnormality. Chromosomal aberrations are seen in about 2.9 to 3.6% of couples presenting with habitual abortions (Gynecol Obstet Mex 1996 Nov) 2/3rd's of these are reciprocal translocations, while 1/3rd being Robertsonian translocation. Parents with chromosomal variance have an increased risk of

spontaneous abortions.

2. Anatomic Abnormalities: Such as congenital uterine defects, cervical incompetance, submucous myomas, Ashermans syndrome, and abnormalities due to diethylstilbesterol in utero. These account for 15% of recurrent abortions in the 1st trimester and for about 33% of those occuring in the 2nd trimester.

   Cervical incompetance accounts for 3% of 1st trimester abortions compared to 30% in the second trimester. Uterine defects account for about 12% in both trimesters - bicornuate uterus and single uterine horn each account for about one third, while septate uterus for another 20 to 25%.

3. Endocrine Dysfunction: Accounts for upto 25% of habitual abortions. These include corpus luteum deficiency, hypothyroidism, poorly controlled diabetes, and polycystic ovarian disease.

   Traditionally, when no other cause for recurrent abortions has been found, corpus luteum defect has been postulated. This diagnosis is made despite the fact that the hormonal abnormality may be the effect rather than the cause of the pregnancy loss.

   Though the association between hypothyroidism and recurrent abortions has been challenged, contrary to all beliefs some patients have responded to thyroid therapy.

   Poorly controlled Diabetes mellitus is associated with a 3 fold increase in the rate of spontaneous abortions. A clear correlation has been demonstrated between elevated glycosylated hemoglobin and spontaneous abortions.

   The prevalence of polycystic ovaries in habitual aborters is about 56%. The link appears to be a hyper-secretion of the leutinizing hormone which is present in 58% of women with PCO. This may act in the following ways:- direct inhibition of the oocyte maturation inhibitor (omi) which leads to the production of physiologically aged oocytes., altered synthesis of endometrial prostaglandins, increasing androgen synthesis by the theca cells, and production of abnormal glycoforms.

4. Immunological Causes: immunological acceptance of the fetus by the mother still remains an enigma. The absence of major histocompatibility antigens has been noted on the syncytiotrophoblast, but class I HLA ABC and class II HLA DR antigens have been found. It has been proposed that maternal recognition of trophoblast lymphocyte cross reactive (TLX) or the blocking antigens is responsible for fetal survival.

   Couples with habitual abortions are more likely to share HLA antigens, this prevents trophoblast recognition and failure to generate blocking antibodies, they have fewer inhibitors of cell mediated immunity, are more likely to have an absence of transplantation antigen, have more likely to have an absence of transplantation antigen, have more fetuses that are transplant antigen compatible, have an increased sharing of transferrin G with their partners, low serum anti cytomegalovirus response, lower lymphocytotoxic antibody titre, and a lower antisperm antibody titre.

   Despite this information, the diagnosis of immunological abnormalities is largely retrospective.

   Autoimmune disorders include Antiphospholipid antibody syndrome, Systemic lupus erythrematosus. 10 to 16% of women with recurrent abortions have antiphopholipids antibodies. Fetal demise can occur at all stages of pregnancy. APA positive women tend to abort at progressively lower gestational ages. The reported fetal loss rate is upto 80% in these women. Alloimmunity includes all causes related to an abnormal maternal immune response to antigens on the placenta of fetal tissue.

5. General disease: Willsons disease, chronic renal disease. The incidence of systemic disease as a cause of habitual abortions is unknown.

Doubtful Causes

1. Anatomical uterine defects :

Retroversion - traditional thinking indicates that retroversion is a cause of habitual abortions. Though a gravid, fixed retroverted uterus may get incarcerated in the pelvis, there is no evidence that suggests that this is a cause of recurrent pregnancy loss.

IntraUterine Adhesions - these are more likely to cause infertility than recurrent abortions

2. Infections: The limited evidence linking infection & recurrent pregnncy loss is anecdotal & generally cannot be reproduced in prospective studies. The probable factors that play a role in the risk of abortion due to infections are the following.

1. Primary exposure during early gestation.
2. Capability of the organism to cause placental infection.
3. Development of an infectious carrier state
4. Immunocompromise caused by immuno suppressants, chemotherapy, steroids or AIDS.

A number of organisms have been implicated like toxoplasmosis, listeria, brucella, chlamydia, mycoplasma, herpes simplex, and cytomegalovirus, ureoplasma ureolyticum.

Toxoplasmosis has been found to cause abortions in later pregnancy, but does not appear to be a significant factor for the habitual aborter. The organisms have been found in 20% of habitual aborters as compared to 21.3% of the controls.

Though Listeria has been definitely associated with recurrent pergnancy loss in animals, their role in humans has not been clearly defined.

3. Endorine disorders:

Untreated adrenal hyperplasia may have an increased risk of recurrent abortions, but the condition by itself is rare. Definite proof of the role of hypothyroidism is not available.

4. General diseases : congenital hypofibrinogenemia, factor XIII deficiency, phenyl ketonuria, glucose - 6 - phosphatase deficiency have been associated with an increased risk of abortions. Other diseases like chronic intestinal problems, Crohn's disease, sickle cell disease and psychiatric disturbances have a doubtful risk though they are more commonly seen.

5. Endometriosis: increased levels of PgF2α is the suggested mechanism. But it has been found that the incidence of abortions is inversely proportionate to the severity of the disease.

6. Environmental causes : herbicides, alcohol, smoking, anaesthetic gases, solvents, heavy metals. The use of video display terminals has not been found to be associated with a higher risk.

In a study conducted by Cauchi et al (AM J Reprod Immunol 1995 Feb) to determine the predictive factors in reccurent spontaneous aborters, it was found that there was a significant association between the number of previous abortions, the length of the previous abortion history & the subfertility index. The subfertility index is a product of the number of spontaneous abortions & the abortion history. For each increase of 10 in the sub fertility index the rate of a successful pregnancy decreased by 40%. There is however little association between the success rate & age, parity or immunotherapy with leucocytes from the husband.

Preimplantation factor (PIF) measured in lymphocyte / platelet binding assay has also been used to predict subsequent abortions (AM J Reprod Immunol 1995 Aug)

Management

The management of recurrent pregnancy loss is confusing and frustrating hindered by the bias of the investigating clinicians and uncontrolled reports found in literature. Using a systematic approach, it is possible to identify a probable cause in over 50% of the couples.

It is valuable, however, to remember that women who have miscarried recurrently from one cause are not protected from a further miscarriage from another cause.

Investigations should be directed towards finding an etiological factor. A careful reproductive history and a three generation pedigree should be taken for both partners. Any family history of congenital abnormalities, early pregnancy losses and chromosomal disorders should be ascertained.

Approach to a Patient with Recurrent Abortions

History to be elicited in between the pregnancies:

From the Female Partner;
Age
Menstrual history
Duration of marriage
Contraception use
Number of previous pregnancies and their outcome.
Gestational age at outcome
Type of Abortions associated with pain
Post abortal curettage
Histopath confirmation of POC
Karyotype of abortions

Past medical history	Diabetes Mellitus
	Thyroid
	Chronic renal disease
	TORCH Infections
Past Surgical history	On genital tract
Family history	Chromosomal disorders
	Congenital anomalies
	Diabetes Mellitus

History of substance abuse

From the Husband

Age
History of previous successful proven fertility
Occupation
Medical illness
Testicular Trauma

Family history	Chronic disease
	Oligo/polyspermia

Substance abuse

On Examination

Mental status
General examination
Vital signs
Stigma of endocrinal / systemic disease
Systemic examination

Per Speculum	Cervial / vaginal infection
	Condition of external Os
Per Vagina	Uterus size, shape, mobility, anomalies Adnexae
	Cervical incompetence / tears

History during Pregnancy

Last Menstrual Period
Previous cycles
Use of oral contraceptives
Use of ovulation inducing agents
Bleeding / pain / pelvic pressure

On Examination

General examination
Uterine size
Evidence of cervical incompetence
Evidence of endocrine disorders

Investigations

Genetic

Parental karyotyping
Karyotyping of abortus / amniotic fluid / amnion / placenta

Anti Phospholipid Antibody Syndrome (APS)

Lupus Anti Coagulant - Activated Partial Thromboplastin Time, Kaolin Clotting Time, dilute Russel Viper Venom Time

Anti Cardiolipin Antibody] Elisa

Indications for screening for APS

All auto-immune diseases
Thrombocytopenia
History of arterial / venous thrombosis
BFP VDRL
Recurrent abortions
All fetal losses > 20 weeks of gestation
Placental abruption
IUGR
Early onset preeclampsia
Chorea gravidarum

Infections which induce APS - Mumps, measles, chicken pox, HIV, Gram negative infections.

Luteal Phase Defect

Endometrial biopsy showing a lag of at least 2 days. EB done on D 25. Lag calculated retrospectively from the onset of subsequent menses.

Midluteal progesterone level <10ng ideally 3 samples got between 4 & 11 days before the next expected menses.

Hypothyroidism

T3, T4, TSH
Thyroid Scan

Diabetes Mellitus

Blood sugar profile
Glycosylated Hb
Assess for endorgan damage

Polycystic Ovaries

FSH LH	High LH, Altered FSH/LH ratio
Ultrasound Scan	Most sensitive - > 10 follicles of at least 8mm surrunded by a echodense stroma.
Laparoscopy	Thick smooth pearly white capsule enlarged
Allo Immune	Mixed lymphocyte asay for HLA typing of both parents.

Syphillis

Screening	VDRL Reactive Protein Reagin
Confirmatory	FTA - Abs Microhaemagglutination assay for T.Ab.

Screen all contacts

Rubella

Hemagglutination inhibition
ELISA
RIA
Immune fluorescent assay

Toxoplasma

Sabin Feldman Dye Test
ELISA
Polymerase Chain Reaction

Chlamydia

Vaginal / Cervical swab
ELISA
Polymerase Chain Reaction
Ligase Chain Reaction

Cytomegalovirus

Viral culture
ELISA

Listeria

Blood culture in acute phase

Uterine Anomalies

Clinical Examination
Ultrasound Scan
Hysterosalpingogram
Sonohysterography - A newer method for screening with upto 100% sensitivity & specificity is Sono hysterography. Here saline is instilled into the uterus

through an endocervically placed balloon catheter with concurrent vaginal sonography.

Hysteroscopy
Laparoscopy

Cervical Incompetance

In between Pregnancy	Easy passage of No. 8 Hegar Dilator
	Olive tipped sound
	Foleys catheter 10cc bulb
	Hysterography
	Balloon hysterography
During pregnancy	Clinical examination
	Ultrasound scan

Herpes

Elisa
Paps smear
Isolation of virus

Embryotoxic Factors

Soluble factors produced in response to sperm and trophoblast which are toxic to embryos.
Serum, Cord blood - Hill A. J. Ecker et al. Obstet. Gynaecol. 1993.
Environmental causes / occupational hazard history
No specific lab tests

Endometriosis

History of dysmenorrhoea / pelvic ureteral pain
Dyspareunia
Infertility
Recurrent abortions

On Examination

NAD
Beading / tenderness on uterosacrals
Nodularity in cul de sac
Fixed Retroverted uterus
Enlarged cystic ovaries

Investigation :	Ultrasound scan
	Laparoscopy

Systemic Lupus Erythromatosus

ANA
LA
LE Cell

Treatment

Women with previous pregnancy losses show a lower quality of life as revealed by the feelings of soial isolation, negative emotions, pain, anxiety etc. The implications of this is that the treating Obstetrician should be aware of these strong feelings & should offer adequate counselling & support in addition to treating the cause of their previous pregnancy losses.

Genetic

Counselling
Donor Sperm/donor eggs
Gene Therapy

Anti Phospholipid Antibodies Syndrome

Mother -	Assess for target organ damage at regular intervals
	Platelet count
	LA monthly
	acl
	Low level Antibodies (acl <60, KCT <250s)
	Monitoring
	Low dose aspirin 75 mg/day
High level antibodies (acl >60 KCT >250s)	
	Monitoring
	Low dose aspirin
	H/o thrombosis, give Heparin 5000-10000 IU S/C
	No H/O thrombosis - Then give Prednisolone 10-20 mg/day to get KCT to below 200 s
Fetus	USG monitoring of growth
	Detection of early abruption
Mother	Regular ANC
	Avoid smoking
	Educate regarding pH, abruptio
	DFKC from 24 wks onwards. If growth retarded
	USG once in 2 weeks + Doppler

CTG	Biophysical profile
Prednisolone	40 mg/day Immunosuppression by inhibiting production of Interleukin 2 by T4 cells. Adverse effects > Cushingoid, acne, adrenal insufficiency, diabetes, candidiasis, hypertension, osteoporosis
Heparin	5000 - 10,000 iu, SC BD Facilitates action of activated thromboplastin Keep AP ++ 1.5 - 2.0 times above normal: Adverse effects - Thrombocytopenea, osteoporosis, bleeding
Aspirin	75 mg / day Inhibits cycle oxygenase in platelets No adverse effects reported
Azothioprine	75 mg/day - 100 mg/day Immunosuppression by purine antibodies Bone marrow depression
Immunoglobulins	0.5 - 4.0 IU/kg body weight / day Inactivates complement T cell suppression Decrease cytokine synthesis

Luteal Phase Deficiency

Progesterone	72 hrs after BBT rise Vaginal 25-50 mg bd I.M. 12.5 - 25 mg daily Till 8-9 weeks gestation Natural progesterone preferred Cheap, easily available No significant adverse effects
Human Chorionic	Gonadotropin - After LH surge 2000-5000 IU every 2-5 days till 12 weeks

Hypothyroidism	Eltroxine
Diabetes Mellitus	Counselling Insulin

Poly Cystic Ovaries

Weight loss
Pretreatment LH suppression - 6 Months of OC Pills
Done regularly with GnRH
Ovulation induction - CC/HMG/HCG
Ovarian drilling
Wedge resection

Allo immunity	Paternal lymphocyte therapy - 77% achieved live pregnancy (Mowbray et. al Lancet 1985) Leucocyte rich donor blood (Unander et al, Am J Obstet gyn 1986) 3 infusions given 4-8 weeks apart Seminal plasma vaginal suppositaries (Stern JJ et al Am J Reprod. Immunol 1992)

Immunotherapy still remains experimental since there is no specific test which will predict the need for treatment. Also the effects on the placenta & fetus remain largely unknown.

3 randomized control trials have failed to show the beneficial effect of immuno therapy.

	Ho H.N. Gill T.J. et al 1991 Am J. Reprod.
Immunol	Cauchi M.N. et al Am J Reprod Immunol 1991
	Christiansen et al. Fertil Steril 1992

Syphillis

Early	(Primary / secondary/latent < 1 yr duration) Benzathine Penicillin 2.4 million units I.V. Repeat, if necessary 1 week later
Late	> 1 yr duration / cardiovascular)

Benzathine Penicillin 2.4 million units I.M. WKLY. for 3 weeks If allergic to Penicillin, Erythromycin or Tetaracycline can be used.

Rubela

No effective treatment
Vaccination - RA 27/3
Avoid pregnancy for 3 months after vaccination

Toxoplasma

* Spiramycin 3g / day from time of seroconversion till delivery
* Spiramycin 3g / day for 3 weeks followed by gap of 2 weeks then repeat from seroconversion till delivery.
* Spiramycin 3g / day + Pyremethamine 25 mg / day + Sulphadoxine 500 mg/day qid followed by spiramycin till delivery
* Clindamycin 1.2 - 4g / day

Indications for Treatment

1. IgM positive
2. 4 fold rise in IgG titre
3. Seroconversion recent

Chlamydia

Erythromycin 500mg QID for 7 days
Amoxycillin 500mg TID for 7 days
Azithromycin 1gm single dose

Cytomegalovirus

No effective treatment
? use of gancyclovir

Listeriosis

Ampicillin + Gentamycin
(Penicillin g, Erythromycin, Rifampicin, Septran)

Herpes

Acyclovir 200 mg 5 times a day for 10 days
Analgesic
Topical anaesthetics

Uterine Anomalies

Uterine septum — Transcervical lysis by hysteroscopy. Can be preceeded by Danazol or GnRH analogues for 2 months to reduce the amount of endometrium, which can obscure view.

Septate Uterus — Modified Jones Metroplasty. The septum is excised as a wedge and the uterus is closed in three layers.

Tompkin's Metroplasty. A single median incision divides the corpus into two. Each lateral septal half is incised and resutured. No septal tissue is removed.

Bicornuate and Didelphic Uteri - Strassman's Metroplasty.

Intra Uterine Adhesions - Excised via hysteroscope.

Cervical Incompetence

Post conceptional

* Shirodkar's stitch - Purse string encirclement of the internal Os with non absorbable material Dacron, Fascia lata, Mercilene
* McDonalds Stitch - Purse string suture with mersilk at the junction of the rugae vagina & smooth cervix at the level of internal os.
* Boyd - Steel wire instead of mersilk
* Wurm - right angled mattress suture with mersilk once cervical effacement had started.
* Benson - trans abdominal serica uterine cerclage done when congenitally short cervix amputated cervix marked scarring after previous unsuccessful cerclage

Multiple cervical defects
Unhealed penetrating forniceal lacerations
Subacute cervicitis
H/D. Previous failed transvaginal cerclage

* Baden - Bridge tracheloplasty
* Vitosky - Use of a Hodge Smith pessary pre conceptional
* Lash - excision of a segment of the cervix at the level of the internal os or repair
* Mann — Isthmic cerclage with nylon
* Page — external unrapping procedure leading to scarification
* Baenes — Electrocauterization

Embryo toxic factor

Progesterone supplementation - Acts

	by immuno suppression.
	Vaginal or I.M.
Environmental causes / Occupation	
	Counselling
Endometriosis	
Mild	No treatment - Analgesics for pain
Moderate & severe	
Surgical	Adhesiolysis, Diathermis, Cystostomies, excision, laser vaporization, presacral neurectomy
	Medical - Combination OCP x 6 mths
	Danazol 400 mg bd x 6 mths
	Prostaglandin inhibitors
Progestogens	MPA 30 mg od x 6 mths
	Megesterol acetate 40 mg od x 6 mths
	Depo MPA 150 mg every 3 months
	Has the disavantage of delayed ovulation after discontinuing therapy.
GnRH agonists	Buserelin - daily 2-4 weeks
	Leuprolide - Monthly
	Can be combined with post menopausal HRT 0.625 mg Premarin + 2.5mg MPA daily
Gestrinone	2.5 - 5.0 mg twice weekly

Systemic Lupus Erythromatosus

Prednisolone 40-60 mg daily.

Current recommendations for early pregnancy monitoring include - prenatal vitamins with folic acid for 3 months preconceptually and 3 months spacing between pregnancy. The pregnancy should be confirmed by a quantitative Beta hCG titre with weekly titres to confirm an adequate rise. A single serum progesterone level at 6-8 weeks confirms adequate progesterone productin in early prgnancy. A Transvaginal scan at 6-8 weeks substantiates fetal development. Cervical checks is necessary, if cervical incompetence is suspected. The patient should be instructed to come in early if abortion threatens.

Studies conducted to see the efficacy for HCG support in recurrent pregnancy loss have shown that in women with oligomenorrhea HCG supplementation has a higher pregnancy success rate.

While assessing the efficacy of treatment for these patients, we need to remember that even without treatment upto 60% of cases are successful in their next pregnancy. Pregnancy rate with treatment has been found to be upto 86%.

Conclusion:

The patient with recurrent pregnancy wastages presents as an anxious frustrated individual on the verge of despair.

Providing reassurance and tender loving care may suffice for couples, who abort for the first or second time. But with the recurrent abortion this approach is less likely to be accepted by the couple. Full investigations are indicated, but still in a majority of cases no explanation is found. Until more knowledge is available from large controlled trials, the couple should be discouraged from empirical treatment.