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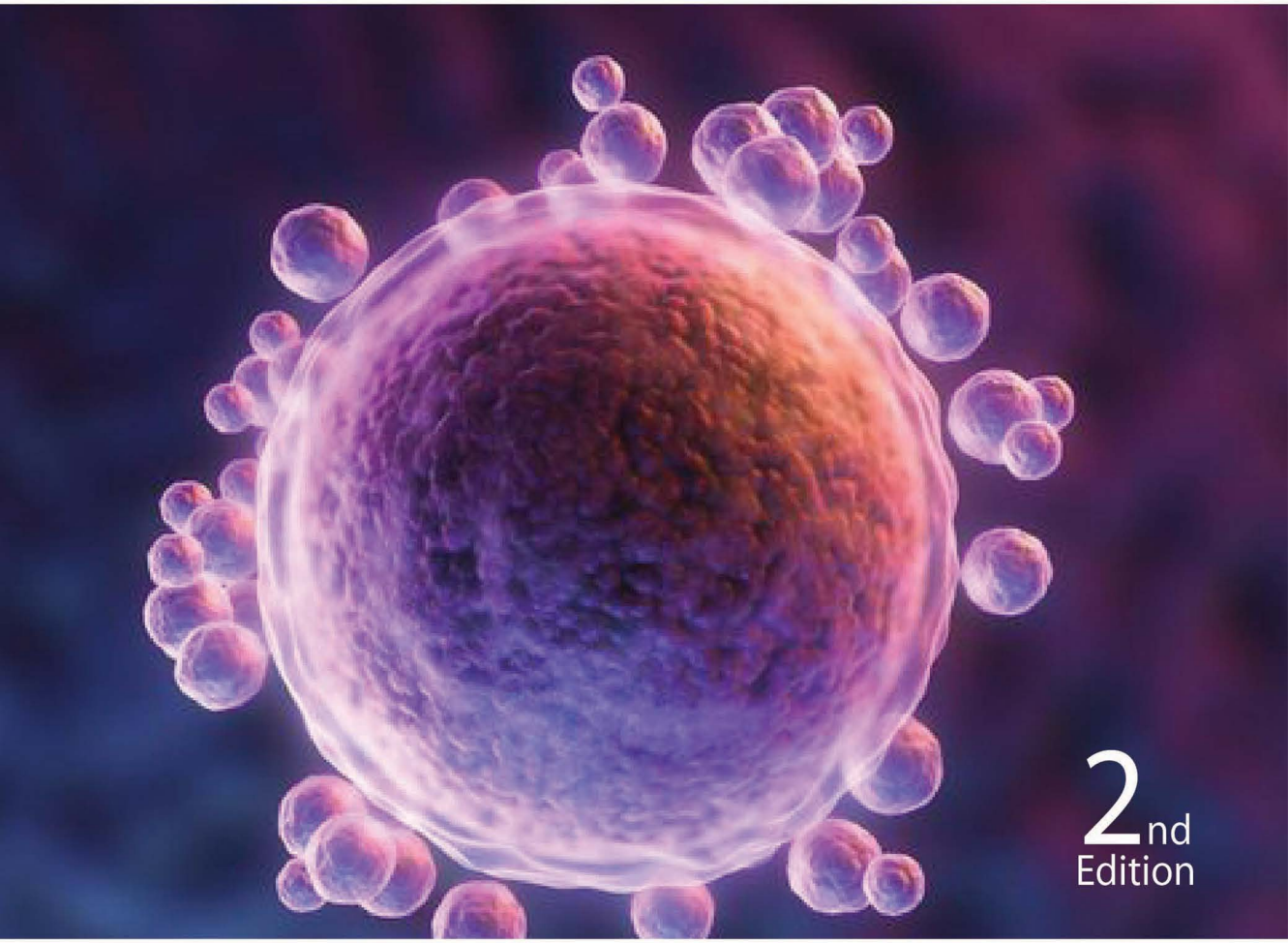

2nd Edition

K Jayakrishnan

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M Subhadra Nair

JAYPEE

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CHAPTER 4

Recurrent Pregnancy Losses in Assisted Reproduction

HJA Carp

Chapter outline

- Causes of Recurrent Pregnancy Loss and Infertility
  - Abnormal Embryo
  - Antiphospholipid Syndrome
  - Alloimmune Factors
- Prognosis
  - Investigation Protocol
- Treatment
  - Progesterone Supplementation
  - hCG Supplementation
  - Aspirin
  - Heparin
  - Immunoglobulin
- Assisted Reproductive Technology as Treatment of Recurrent Pregnancy Loss
  - Pregestational Screening
  - Gamete Donation
  - Surrogacy

INTRODUCTION

Although recurrent pregnancy loss (RPL) is a different condition to infertility, there is an association between the two conditions. There may be similar causes, one affects the prognosis of the other, and often treatment which is used for one may be used to treat the other. Concurrent infertility is found in 32% of RPL patients. In the author's database of 2500 patients with RPL, 74 patients were referred to assisted reproductive technology (ART) for subsequent infertility. Similarly, 182 ART patients have been assessed with RPL after ART. The incidence of missed abortion is 15 percent after ART (Schieve et al. 2003), which does not appear to be increased above that of the general population. This chapter will examine the influence of one condition on the other.

CAUSES OF RECURRENT PREGNANCY LOSS AND INFERTILITY

Both RPL and infertility may be caused by embryonic abnormalities or a hostile maternal environment. Table 4.1 shows the generally accepted causes of both conditions.

Abnormal Embryo

Structural malformations may cause pregnancy loss presenting as miscarriage. Embryoscopy has shown developmental defects in 200/233 missed abortions (85%) (Philipp et al., 2003), including: anencephaly, encephalocele, spina bifida, syndactyly, pseudosyndactyly, polydactyly, cleft hand and cleft lip. However, as 70% of miscarriages are blighted ova in which ultrasound only

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Table 4.1: Causes of infertility and pregnancy loss.

Recurrent pregnancy loss	*Implantation failure*
Abnormal embryo	Abnormal embryo
Structural anomalies incompatible with life	Chromosomal anomalies
Chromosomal anomalies	
Hostile maternal environment	Hostile maternal environment
Uterine	Endocrine
APS	Defects in endometrial receptivity
Thrombophilia	
Alloimmune	
Infection	
Endocrine	

APS: antiphospholipid antibody syndrome

visualizes empty sac, it is often impossible to detect these malformations if present. In implantation failure, there can be no structural malformations.

Embryonic chromosomal aberrations may be responsible for both RPL and infertility. Five reports have assessed chromosomal aberrations in recurrent miscarriage and have reported that 19–60% of abortuses are chromosomally abnormal in women with recurrent miscarriage. The incidence is inversely proportional to the number of miscarriages, and rises with maternal age. The possibility of chromosomally aberrant chromosomes has also been assesses in ART using pregestational diagnosis (PGD) techniques. About 29% of embryos which appear morphologically normal have been found to be chromosomally abnormal (Munne et al., 1995). Even in those embryos developing to blastocysts, 29% have been reported to be mosaic.

Rubio et al. (2003) have described the effect of different chromosomal abnormalities on embryo development. Only 20.2% of autosomal monosomies developed into blastocysts, whereas embryos with monosomy X developed similarly to normal embryos. Trisomies also impaired embryo development, only 34.7% formed blastocysts. Most haploid embryos arrested before cavitation, and triploid and tetraploid embryos had lower rates of development to the blastocyst stage. Hence, the more severe cases of aneuploidy might be more likely to present clinically as infertility, and the less severe aneuploidies may present as recurrent miscarriage.

Antiphospholipid Syndrome

Antiphospholipid antibodies (aPL) such as lupus anticoagulant and anticardiolipin antibodies are associated with RPL. There is also evidence that additional antibodies may be associated with both pregnancy loss and infertility. In RPL, fetal demise is thought to be secondary to thrombosis in the small vessels of the placenta. Women with antiphospholipid antibody syndrome (APS) are at a high risk for pre-eclampsia, intrauterine growth retardation, fetal distress, stillbirth, and maternal autoimmune phenomena. Today, aPL are also known to have their effects by binding to trophoblast, inhibiting trophoblast differentiation "*in vitro*", invasiveness and human choriomic gonadotropin (hCG) secretion. Hence, the question arises whether aPL may also be involved in infertility. Bakimer et al. (1992), immunized BALB/c mice with human monoclonal anticardiolipin antibodies (aCA). Lower fecundity rate after immunization (21% vs. 48%) ($P < .005$). Shoenfeld et al. (2006) found a significantly higher prevalence of aPL in infertile patients (OR = 5.11, CI 1.18–25.35). Although there are reports of increased prevalences of aPL in prolonged infertility and IVF failure, the American Society of Reproductive Medicine has issued a practice bulletin in 1999 on this issue based on a systematic review. The clinical pregnancy and live birth rates were

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57% and 46% respectively, in the aPL positive patients, compared with 49.2% and 42.9%, respectively, in the aPL negative patients. The bulletin concluded that aPL testing is not warranted in patients undergoing *in-vitro* fertilization (IVF), and treatment is not indicated in seropositive patients. The same conclusion was drawn by Hornstein et al. (2000), after a meta-analysis of studies which assessed aPL and IVF success.

However, there are other aPL in addition to anticardiolipin antibodies and lupus anticoagulant. Antiphosphatidyl ethanolamine and antiphosphatidyl serine antibodies may be relevant in IVF failure. Antiphosphatidyl ethanolamine antibodies may be risk factor for early fetal losses and infertility as they affect trophoblast formation. Antiphosphatidyl serine antibodies may be induced when phosphatidyl serine is exteriorized due to apoptosis.

Alloimmune Factors

Alloimmune factors such as cytokines and natural killer (NK) cells, have been linked to both RPL and infertility. NK cells physiologically accumulate in the decidua in the first trimester of pregnancy. Their role may be immunosurveillance, mediation of angiogenesis or remodeling of spiral arteries to uteroplacental arteries. NK cells are part of the innate immune system. Their response is not dependent on recognizing a specific antigen. Although the trophoblast is semi-allogeneic and contains foreign paternal antigens, NK cells do not normally attack the trophoblast. However, if NK cells become activated by cytokines, they can attack the trophoblast causing apoptosis. Increased numbers of NK cells have been found in the peripheral blood of patients with RPL (Emmer et al, 2000). Additionally, increased concentrations of NK cells have been found in luteal phase endometrial biopsies in RPL (Clifford et al., 2000). Aoki et al. (1995) first described the clinical relevance of NK cells in 68 women with 2 or more miscarriages, and compared them to 47 control patients. The patients with high NK activity had a 71% abortion rate compared to 20% in the low NK activity patients. They also tended to abort genetically normal embryos. Only 17% of aborted embryos had karyotypic aberrations, compared to 60% in women with low number of NK cells. Coulam and Beaman (1995) have reported that when NK cells are above 12% of total lymphocytes, there is an 87% predictive value for a pregnancy loss. These patients also tend to lose genetically normal embryos as opposed to the women with normal NK cells who lose genetically abnormal embryos.

Cytokines can mediate NK cell activity. TNFα can activate NK cells to attack the trophoblast. NK mediated attack can lead to implantation failure or pregnancy loss. $TGFB_2$ inhibits NK activation. In addition to the action on NK cells, cytokines affect each stage of implantation and embryonic development. There are cytokines preventing implantation such as IL-18, and cytokines which are essential for implantation, such as leukemia inhibitory factor (LIF). LIF also influences cytotrophoblast differentiation and invasion, as does IL-3. IL-15 increases trophoblast invasion, modulates MMP-1 and maintains uterine NK cells. Vascular endo thelial growth factor (VEGF) is responsible for establishing the blood supply to the developing conceptus. There are cytokines affecting trophoblast proliferation such as GM-CSF, and TGFβ. Epidermal growth factor (EGF) affects hormone secretion (hPL and hCG) by the trophoblast. IFNγ influences the remodeling of spiral arteries to uteroplacental arteries. IL-4 and IL-10 inhibit coagulation. Coagulation is enhanced by TNFα and IL-6. Therefore, it can be seen that the right cytokine balance is essential for both implantation, hormonal secretion in pregnancy, maintenance of blood supply, and prevention of excessive coagulation. All of these may present as infertility or pregnancy loss.

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Antiphospholipid antibodies also act through cytokines. IL-3 and IFNγ are decreased in automune polyendocrine syndrome (APS). TNFα and IL-6 are elevated in APS.

PROGNOSIS

As stated above, the incidence of missed abortion is 15% after ART (Schieve et al., 2003). This incidence is not greater to that of the general population; hence the prognostic factors affecting the outcome of pregnancy after RPL are the same as RPL without ART. The prognosis varies according to the following features, each of which increases the chance of another miscarriage—advanced maternal age, a higher number of previous miscarriages, primary (all pregnancies have terminated as miscarriage), as opposed to secondary abortions (live birth followed by a string of miscarriages), concurrent infertility, and a previous eukaryotypic abortion (Carp, 2001 a). The number of previous miscarriages seems to be the most important predictive factor. Concurrent infertility is a predictive factor, worsening the prognosis. Concurrent infertility refers to RPL patients who develop infertility, and who may or may not require ART. This is a different group of patients to those described by Schieve et al. (2003), who are ART patients who have one subsequent missed abortion.

Investigation Protocol

An investigation protocol should indicate the investigations required to reach a diagnosis. There is however, disagreementy when investigation should commence. The American College of Obstetricians and Gynecologists practice bulletin states that women with two miscarriages should be investigated, however, the Royal College and ESHRE suggest that investigation be reserved for patients with three or more pregnancy losses. The author uses a different approach depending on whether the prognosis is good, medium or poor. The different approaches for different patients have been published elsewhere (Carp, 2007). In brief, "Good Prognosis Patients" refers to young women with two or three first trimester miscarriages. They probably require little investigation or treatment. However, they do require supportive care. In the event of another miscarriage, further investigations should be performed including fetal karyotyping. It is doubtful if "good prognosis" patients require pharmacological support.

"Medium Prognosis Patients" are those with three or four miscarriages. The prognosis is approximately 60% for a live birth after three miscarriages (40% after four miscarriages). Treatment should be based on the cause. However, despite extensive investigations, the cause may remain elusive. The author assesses the uterus by hysteroscopy or three dimensional ultrasound, if these investigations have not been performed for infertility. An autoantibody screen for antinuclear antibody, B_2-glycoprotein 1 dependent anticardiolipin antibody and lupus anticoagulant is performed, together with screening for the hereditary thrombophilias. Thyroid function and a glucose challenge test are ordered if indicated. Treatment is usually empiric. If there is a uterine septum, it can be resected. Ogasawara et al. (2009), showed in a case control study that uterine anomalies impacted on progression of normal pregnancies. If aPL or hereditary thrombophilias are present anticoagulants such as low molecular weight heparins are effective and safe. Hormone supplements such as hCG are also used empirically if there is no hyperstimulation after ART.

We define "Poor Prognosis Patients" as those with five or more miscarriages. They are poorly described in the literature, and have been assessed in few trials. These patients have usually had extensive investigations and empirical treatment. After five or more miscarriages, the likelihood

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of fetal chromosomal aberrations is less than after three miscarriages. In these patients, we perform alloimmune testing including a cytotoxic cross match between maternal serum and paternal cells to detect antipaternal complement dependent antibodies (APCA) and possibly assessment of NK cells. In poor prognosis patients in whom other forms of treatment have failed intravenous immunoglobulin can be effective (Carp et al., 2001 b).

TREATMENT

Similar treatment regimens are often used for both RPL and ART. Additionally ART is often used as a means of treatment for RPL. However, all forms of treatment are empirical if the karyotype of the embryo is unknown. Some of these treatment regimens are described below.

Progesterone Supplementation

Progesterone supplementation has been used for over fifty years to prevent miscarriage. The logic of progesterone support is based on the premise that lutectomy causes abortion if performed prior to seven weeks of gestation. Mifepristone blocks progesterone receptors, leading to fetal death and placental separation. Hence, a defective corpus luteum may produce insufficient levels of progesterone, for endometrial ripening, implantation or placentation. Progesterone enhances implantation and affects cytokine balance (inhibits IFNγ and TNFα production, and increases levels of IL-4). Additionally, progesterone inhibits NK activity at the feto-maternal interface, inhibits the release of arachidonic acid, favors the production of asymmetric, pregnancy-protecting antibodies and prevents myometrial contractility. Although progesterone supplementation is widely used routinely in most IVF programs, a large meta-analysis of data from 11 placebo controlled trials (Haas and Ramsey, 2009) concluded that there is no evidence to support routine use of progestogen to prevent miscarriage in early to mid-pregnancy. In RPL, Daya (1989) reported in a meta-analysis of three studies that progesterone supplementation was associated with a statistically significant increase in the live birth rate (OR = 3.09, CI, 1.28–7.52). However, the three trials in the meta-analysis were performed between 1953-1964. At that time there was no early ultrasound screening available; hence, progesterone may have been administered to patients with nonviable pregnancies, raising doubts about the meta-analysis' validity today.

There are also other arguments against progesterone supplementation. Diagnosis is usually by endometrial biopsy two days prior to menstruation and histologically dated. If the histology lags more than two days behind the chronological age luteal deficiency is thought to occur. However, if dating is determined by ultrasonic monitoring of follicular size and biopsy timed to 12 days later, the incidence is only 4% (Peters et al., 1992). Plasma progesterone levels are an unreliable test of luteal function as progesterone is secreted in a pulsatile fashion, and blood may be drawn at a pulse peak or nadir. Additionally, low progesterone levels may be a sign of failing pregnancy from chromosomal or other disorders. Progesterone is often used for luteal support in ART. If RPL follows ART, progesterone supplementation will not be appropriate treatment.

hCG Supplementation

Human chorionic gonadotropin (hCG) supplementation is often used in RPL. It is the only treatment for RPL described to have an effect in the Cochrane database (Scott and Pattison, 2000). When hCG supplementation is used, Scott and Pattison's systematic review (2000) showed a statistically significant benefit of 26.3%, (OR for miscarriage = 0.26, CI 0.14–0.52).

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The hCG has numerous actions in pregnancy. Regular hCG stimulates the corpus luteum to secrete, progesterone, relaxin and prostaglandin E2 production. hCG influences TNFα and IL-6 secretion. The hyperglycosylated form of hCG is autocrine acting on the trophoblast to increase invasiveness. hCG is involved in differentiation of endometrial stromal cells to decidua, regulates smooth muscle cell gap junctions in the pregnant human myometrium inhibiting myometrial contractions, and hCG promotes angiogenesis via up regulation of VEGF. hCG also has immunoregulatory roles, including the prevention of T-cell activation at maternal-fetal interface. hCG influences the secretion of TNFα, IL-6, IL-1β and IL-2. However, it is interesting to note that all trials of hCG have used urinary derived hCG rather than the newer recombinant form. Urinary hCG contains Leukemia inhibitory bactor (LIF) which regulates trophoblast differentiation, and is essential for implantation. hCG is not usually used in ART cycles except for inducing luteinization of the follicle approximately 36 hours prior to ovum pick up. There are a few reports of using hCG for ovum ripening, but the effect has not been assessed on RPL. hCG supplementation cannot be used if ovarian hyperstimulation occurs after ART as hCG will worsen the effects of hyperstimulation.

In the authors series (unpublished), in "poor prognosis" patients with five or more recurrent miscarriages, there was an absolute benefit 34% after using hCG, which is statistically significant, (OR = 4.33, 95% CI 1.7–11.3).

Aspirin

Aspirin has been used as a fertility inducing agent. However, the literature is divided on the efficacy of aspirin in improving uterine blood flow or pregnancy rates. A recent meta-analysis by Daya et al. (2006), stated that, "Given the lack of efficacy and the potential for harmful effects to both the patient and her offspring, low-dose aspirin should not be administered to infertile women undergoing treatment with assisted reproduction". Aspirin is also in wide use for treating APS, where combined with heparin it forms standard treatment. However, there is not one single report in the literature which shows that aspirin has any beneficial effect. There are three papers which have compared the use of aspirin to placebo. Not one of the three papers showed aspirin to have any effect on the subsequent live birth rate. The three papers have been combined in a meta-analysis (Empson et al., 2002), which also showed aspirin to have no effect on the live birth rate. There is only one prospective randomized trial of aspirin for the prevention of miscarriage in unexplained RPL (Tulppala et al., 1997). Twenty seven women were randomized to receive aspirin, and 27 received placebo. There was no difference in the live birth rate, or the incidence of late obstetric complications. The authors concluded, "Low dose aspirin is ineffective in the prevention of miscarriage in recurrent spontaneous abortion".

Heparin

Heparin and the low molecular weight heparins have anticoagulant effects, and are therefore widely used in the antiphospholipid syndrome, and have come into use in hereditary thrombophilias when associated with RPL. In antiphospholipid syndrome a meta-analysis of three trials which compared the effect of aspirin to aspirin with the addition of heparin showed a common odds ratio of 2.63 in favor of heparin (95% CI 1.46–4.75) (Carp, 2004). Heparin also improves the live birth rate in hereditary thrombophilias (Carp et al., 2003).

In addition to the anticoagulant effects, heparins have anti-inflammatory effects. Heparins inhibit TNFα production, and increase serum TNFα binding protein, thereby protecting against the systemic

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harmful manifestations of TNFα. Heparin inhibits apoptosis of villous trophoblast induced by IFNγ and TNFα. Thrombosis results in vein wall inflammatory response. Heparin limits the anti-inflammatory response. *In vitro*, heparin restores ability of trophoblast to secrete hCG, which is inhibited by aPL. Due to the theoretical possibility that the anti-inflammatory effects of heparin may be relevant in unexplained RPL, heparin has been assessed in unexplained recurrent pregnancy loss. In the author's study (Dolitzky et al., 2006), 104 patients were randomized to receive either enoxaparin or aspirin. The live birth rate was similar in both groups of pateints (RR = 1.10; CI, 0.63–1.92). As aspirin is ineffective, enoxaparin offered no additional advantage.

Immunoglobulin

Intravenous immunoglobulin (IVIg) has been used for its immune modulating effects in both RPL and to increase the implantation rate after numerous cycles of ART. IVIg modulates antigen presentation, and B and T lymphocyte function. IVIg inhibits the action of antibodies by either the interaction of the Fc portion of immunoglobulin with Fc receptors, or the Fab receptors. IVIg can also itself act as an anti-idiotypic antibody. Additionally IVIg modulates cytokine effects, and depresses the killing activity of NK cells.

In RPL, IVIg has been used in aPL related pregnancy loss, and in unexplained pregnancy loss. In unexplained RPL a large meta-analysis (Porter et al., 2006) in the Cochrane database has not shown IVIg to confer benefit. However, the papers assessed in Porter et al. (2006), meta-analysis did not correct the results for fetal chromosomal aberrations. IVIg could not to be expected to benefit patients losing chromosomally abnormal embryos, or if administration commenced after fetal demise had occurred, which is the case in some of the randomized trials. A more recent meta-analysis by Hutton (2006), has found a statistically significant increase of 22% in the live birth rate when IVIg was administered prior to pregnancy, but not in the trials when IVIg was only administered in pregnancy (possibly after embryonic demise).

In recurrent implantation failure similar mechanisms may operate as in RPL. Hence IVIg has been used in an attempt to increase the pregnancy rate after previously failed ART. Again the literature is divided on the results. As stated above, *in vitro* karyotyping of the embryos of couples with implantation failure has shown that up to 66% may be chromosomally abnormal. As in RPL, IVIg cannot be expected to enhance the implantation of chromosomally abnormal embryos. Clark et al. (2006) have performed a meta-analysis of 3 randomized trials of IVIg in IVF failure. There was a significant increase in the live birth rate per woman (OR = 2.55, 95% CI 1.19-5.49), with a benefit of 16.7% (P = 0.012).

ASSISTED REPRODUCTIVE TECHNOLOGY AS TREATMENT OF RECURRENT PREGNANCY LOSS

Assisted reproductive technology (ART) techniques are often used to treat RPL. These techniques include pregestational screening (PGS) gamete donation and surrogacy. The first question is whether ART is required at all. As stated above, "good prognosis" patients probably require no active treatment. ART should probably be reserved for the patients with a poor prognosis. Some of the indications and pitfalls are described below.

Pregestational Screening

Pregestational screening (PGS) is based on the premise that RPL is due to chromosomal aberrations and that the patient should be given a eukaryotypic embryo. However, the

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current techniques used for PGS (FISH or PCR) can be applied to only five, possibly seven or a maximum of 9 DNA probes. Therefore, screening is performed for the most common chromosomal aberrations. Chromosomes 13, 16, 18, 21, and X and Y are the chromosomes which are most commonly assessed. Hence, PGS can exclude miscarriages due to 16 and 21 trisomies and XO. However, PGS could miss a chromosomal aberration in a chromosome which was not assessed. If a chromosomal aberration had been diagnosed in a previous miscarriage, PGD could be used for the specific chromosome which was associated with the previous miscarriage and PGS for the remaining chromosomes. In an ideal situation, the entire genome will be assessed. Microarrays using CGH techniques are becoming available to assess the entire genome, but at present the arrays are not sufficiently developed and too expensive to be used on a routine clinical basis. At the present time, the live birth rate per pregnancy does seem to be increased after PGS, saving the patient from further heartbreak from further miscarriages. RPL is probably only indication for which ART is used in fertile patients. However, the pregnancy rate is about 25–30 percent as in infertile patients. Additionally, the pregnancy rate is lowered after PGS (Mastenbroek et al., 2007). It seems that not all embryos survive the biopsy required for PGS; therefore many cases of RPL may be converted to implantation failure. Hence, the live birth rate per patient is certainly not increased. The author does however recommend pregestational diagnosis in cases of repeat fetal aneuploidy, or when there are parental chromosomal aberrations with an associated aberration in the fetus.

Gamete Donation

The series on ovum donation in the literature contain little information on ovum donation as treatmrnt for RPL. The Tel Hashomer registry shows 4 cases of egg donation if 2500 patients in the RPL registry. The author has used ovum donation for a patient age 46 years with no children and six previous miscarriages. Embryonic karyotyping had been performed on three of the abortuses. All three were karyotypically abnormal with different aberrations in each miscarriage. Ovum donation was chosen as the patient's age was thought to preclude a good outcome from IVF. Additionally, with three different embryonic chromosomal aberrations in the past, it was unclear which chromosomes should be screened. Ovum donation is probably indicated for only isolated patients with RPL. If all embryos are found to be abnormal at PGS, ovum donation may be indicated.

There are no series in the literature on the use of sperm donation for RPL. The Tel Hashomer registry shows 62 cases in which there was a change of male partner. Twenty-two patients had three partners, one patient had five partners. Changing the male partner did not prevent subsequent miscarriages. The logic of sperm donation is based on the fact that there is a significantly increased incidence of sperm diploidy and disomy for chromosomes 13, 18, 21, X, and Y in men whose partners had RPL compared to controls (0.84 vs 0.37%) (Rubio et al., 1999). Increases in disomy incidence have been related to increased aneuploidy in the offspring. However, in the current state of knowledge, sperm donation does not seem indicated for RPL.

Surrogacy

Surrogacy is also a technique which involves intensive treatment with ART techniques. Surrogacy is fraught with many legal and social problems, and is also only available in certain countries. The procedure is therefore only used for isolated patients with a "poor prognosis". The author has advised surrogacy in a secondary aborter with 12 consecutive miscarriages, and a primary aborter with 8

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previous pregnancy losses. In both cases the surrogate delivered normal twins. Raziel et al (2000), reported a normal live birth in a patient with 24 prior pregnancy losses. The logic of surrogacy in patients with large numbers of miscarriages is due to the poor prognosis and low incidence of chromosomal aberrations.

CONCLUSION

Although there is an overlap between ART and RPL, both are distinct and different clinical entities. There may be similar causes of both conditions with more mild cases presenting with RPL whereas the more severe cases may present with infertility. Hence, some of the treatment modalities are similar. However, as RPL is not more common after ART, RPL patients should be investigated and treated as RPL patients who have not required ART. As many as one-third of RPL patients do have periods of subfertility, and some patients may require ART techniques. At present many treatment modalities used for ART failure and RPL are somewhat empiric, and will continue to be so, until patients are investigated accurately for either maternal or embryonic chromosomal aberrations as causes for RPL or infertility.

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Dr Jayakrishnan has several national and international papers to his credit and has conducted three research trials under the Department State Science and Technology. He has won Dr RKK Thampan Gold Medal in 1983 and the prestigious FOGSI Corion award for the best scientific paper in the senior category in 1996 and has also chaired the FOGSI Oncology and Trophoblastic Tumours Committee from 2001-2004.

Knowledge is to be shared. Dr Jayakrishnan is a firm believer in this concept and to further this he has conducted several live workshops on Laparoscopy, ART and Ultrasound. Every year, he conducts a live workshop at his institution. He is also the Organizing Chairperson of Advances in Obstetrics, Gynecology and Reproductive Medicine, an International Congress, which is now in its 12th year. Being the Secretary of Trivandrum Obstetrics and Gynecology Club, he engages in academic activities every month for the benefit of fellow Obstetricians and Gynecologists.

Dr Jayakrishnan has also authored Practical Insights in Infertility Management, which gives a quick clinical overview of patient management. Among his several achievements are the birth of the first ICSI baby with sperm retrieved by TESA, South Kerala, India, first ICSI pregnancy with GnRH antagonist reported in South India, and the first baby born from a cryopreserved embryo in South Kerala. With over 20 years of teaching experience and 30 years of clinical experience, he can now rightfully be called an expert in this field.

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