Chapter 6
Early Pregnancy Support: Evidence-Based Management

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Introduction

The physiology of very early pregnancy is a complex mechanism that happens over a narrow window of opportunity against a background of synchronised hormonal and immune factors that lead up to the adequate preparation of the endometrium for the implanting embryo. The peak of the LH surge precedes ovulation by 10–12 h initiated by the raise in the levels of oestrogen. The endometrium transforms into a highly modified endometrium referred as decidua. The decidualisation is dependent on oestrogen, progesterone and other factors secreted by the implanting blastocyst and are complete with the implantation.

The endometrial glands exhibit extensive coiling and luminal secretions become visible. Epithelial cells show decreased microvilli and cilia along with appearances of luminal protrusions of the apical cell surface, referred to as the pinopodes, which are important in preparation for the blastocyst to implant. The crucial steps of successful implantation are detailed in Table 6.1.

Failure of implantation can present as subfertility or miscarriage. Despite advances in understanding the biological and immunological mechanisms underpinning early pregnancy there is a lack of good quality evidence detailing optimal early pregnancy support. We will detail the evidence for the advice that does exist to improve early pregnancy outcomes once pregnancy is achieved. The discussion focuses on the four key elements (Fig. 6.1) throughout the chapter: life style advice

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Table 6.1 Crucial initial steps for successful implantation

Apposition – initial embryo contact with the endometrium
Adhesion – further contact of embryo and endometrium
Invasion – of the developing embryo to the endometrium and inner third of the myometrium

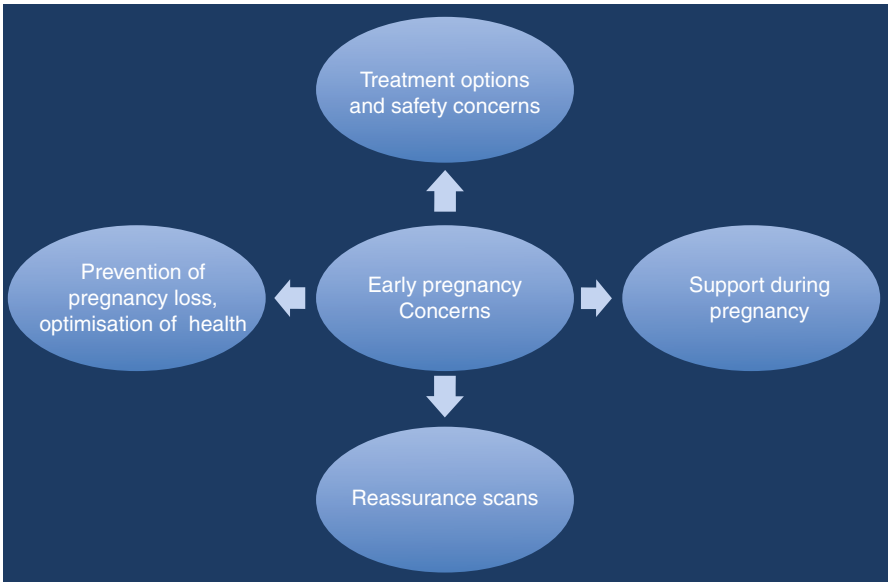

Fig. 6.1 Outline of the expectations of pregnant women from the healthcare professionals [1–7]

to optimise health, pharmacological interventions and safety, ultrasound for reassurance and supportive care during pregnancy.

Life Style Advice

There is information overload regarding life style choices and advice with conflicting headline grabbing evidence presented to women and their partners. The role of clinical staff supporting women is to present the current evidence in relation to those options which enables the women to choose effectively. The most common choices are included in the discussion that follows.

Smoking

There is a dose dependent association between smoking and outcomes such as abruption, stillbirth, recurrent pregnancy loss, decline in ovarian reserve and

fertility, intrauterine growth restriction and placental insufficiency. The evidence is particularly strong with smoking > 20 cigarettes per day. The recommendation is that women stop smoking in pregnancy and evidence suggests that those that do are likely to permanently quit smoking. A review comparing different options of nicotine replacement to help women to stop suggests that after the exclusion of studies with bias, there is no difference in the fetal outcomes between the treatment and the placebo group [8]. The SNAP trial of nicotine replacement reported that there was survival without developmental disorder at the 2 year follow up for babies, making this a safe option for women, but no more likely to be successful than placebo [9].

Use of E-Cigarettes

There is heavy public advertising and marketing of e-cigarettes as a safe alternative to smoking. Though e-cigarettes reduce the harm from carbon monoxide, carcinogens and toxins that contribute to lung cancer, e-cigarettes are still addictive secondary to nicotine release. A published article from 2016 confirms the positive effect of reduction of harm secondary to the carcinogens and toxins in the smoke [10]. There is no published evidence of benefit of use in pregnant women. Until more evidence is available, the advice would be not to recommend e-cigarettes due to variable amounts of caffeine and absorption of inhalational agents of unproven safety.

Alcohol

Alcohol affects fertility and pregnancy outcomes in a dose dependent manner with the well recognised fetal alcohol syndrome relating to excessive alcohol consumption in pregnancy. Consumption of greater than 7 units of alcohol/week is associated with growth restriction and can lead to increased risk of behavioural problems and learning difficulties in children [11]. The current national guidelines also comments that there is no health benefit related to alcohol [12]. Standard advice should be to stop alcohol consumption ideally prior to a planned pregnancy and that there is no safe limit in pregnancy.

Exercise

There is no published evidence to suggest an adverse pregnancy outcome secondary to excessive exercise. Due to the detrimental effects of obesity in pregnancy the advice is to continue with moderate exercise during pregnancy. The review of the effect of aerobic exercise on pregnancy is that it improves maternal fitness [13].

Vitamin Supplementation

Folic Acid

Folic acid is recommended as a pre-conception vitamin supplementation from the time of trying for a pregnancy up to the end of the first trimester in order to prevent neural tube defects. Folic acid deficiency can also contribute to anaemia in the mother.

The Cochrane review of Folic acid supplementation in pregnancy (2013) [14] looked into the evidence from 31 trials (involving 17,771 women) regarding folic acid supplements during pregnancy and the effect on the baby. Whilst there was beneficial improvement in folate indicators in the mother, there was no reduction in the risk of preterm births, low birth weight, stillbirth and neonatal death. The review also did not show any impact of folate supplementation on improving mean birth weight and the mother's mean hemoglobin levels during pregnancy compared with taking a placebo.

The Cochrane review of the effects of folic acid supplementation pre-pregnancy to 12 weeks of pregnancy (2015) [15] found evidence of reduction of the occurrence of both first and second time occurrence of neural tube defects (NTDs). However, there was insufficient evidence to determine if it prevents other defects such as cleft lip with or without cleft palate and congenital cardiovascular disorders.

There were insufficient data to evaluate the effects of folic acid supplementation in prevention of miscarriage, though the quality of evidence was rated as moderate. The data from the Folic acid supplementation during pregnancy [14] review also did not find any conclusive evidence regarding the benefit of folic acid in the prevention of pregnancy loss.

High dose folate is indicated certain condition such as previous NTDs, epilepsy, obesity, MHTFR mutation, sickle cell disease and for women living in areas of high prevalence of malaria. In the absence of these specific factors there are no beneficial effects of high dose folic acid supplementation and concern in some women that this may be harmful by masking vitamin b12 deficiency.

Vitamin D

There is an association between vitamin D deficiency and miscarriage, but no causality has been established. A recent study has established that up to 50% of the population in the UK has vitamin D deficiency with a higher prevalence in obese women. Routine calcium and vitamin D supplementation is recommended for pregnant women due to the prevalence and the increased demand of calcium metabolism during pregnancy. Vitamin D is essential for calcium homeostasis and calcium metabolism [16].

A Cochrane review [16] included 15 randomised controlled trials involving 2833 women. Nine trials compared the effects of vitamin D alone with no supplementation

or a placebo and six trials compared the effects of vitamin D and calcium with no supplementation.

With vitamin D supplementation, the 25-hydroxyvitamin D concentrations at term improve. This reduces the risk of a low birth weight baby (less than 2500 g) and of both preterm delivery less than 37 weeks and developing high blood pressure.

Data on adverse effects for the mother were not well reported. The authors conclude that further randomised trials are required to confirm the effects of vitamin D supplementation and effects on birth weight and blood pressure.

It is unclear if routine supplementation should be recommended during pregnancy.

Caffeine Intake

There is a dose related effect on pregnancy with an increased risk of miscarriage at higher levels. Women should be advised to limit the amount of caffeine to 150 mg/day; equivalent to two cups of normal coffee or three cups of black tea. One study has shown an adverse profile if levels are greater than 300 mg/day [17]. However, the Cochrane review concluded that there was insufficient evidence to correlate the fetal outcomes with maternal caffeine consumption due to the low quality of the studies [18].

Complimentary Therapy

Acupuncture is a well-established mode of complimentary therapy that aims at helping women cope with the stress of subfertility, miscarriage and pregnancy. There are well-established studies that have shown improvements in coping with stress after acupuncture but not in the prevention of miscarriage [19].

Weight

Reproductive outcomes are worse in both underweight (BMI < 18) and obese women (BMI > 30). Any further excessive weight gain in obese women accentuates the adverse perinatal and neonatal outcomes. There is an increased risk of intra-uterine growth restriction, stillbirth, operative deliveries and increased morbidity secondary to infection and thromboembolism. Unfortunately diet and exercise interventions in pregnancy have not shown an impact on neonatal outcome (Cochrane meta-analysis 2015) [20].

However, lifestyle interventions do reduce excessive maternal weight gain and development of maternal hypertension and possibly reduce the risk of caesarean section. Therefore pre-pregnancy advice on diet and exercise to women with high BMI should be routine.

There is no established safety profile for appetite suppressants in pregnancy. The recently published EMPOWAR study [21] did not show any benefit in terms neonatal outcomes for metformin supplementation in women with obesity. The study published in *NEJM* randomised women with BMI > 35 to metformin supplementation or placebo showed a reduction in maternal weight gain but no difference in the neonatal weight in the treatment arm [22].

Pharmacological Interventions to Support Pregnancy

There is a wealth of information and treatment options available to women who undergo ART preconception and during their pregnancy. The only ones of proven benefits are for the following:

- Luteal phase support with progesterone during IVF
- Use of heparin in pregnancy for women with acquired thrombophilia
- Thyroxine in women with clinical hypothyroidism

Progesterone

The Cochrane review suggests that luteal phase progesterone during assisted reproduction improves pregnancy and live birth rates [23]. However, once pregnancy is achieved it is less clear when to discontinue the treatment. Offering luteal phase support for an extended period of time do not appear to result in more clinical benefits, or to cause more harm, than a short period of luteal phase support. While the evidence on this is limited, NICE suggests that it is biologically plausibile for luteal phase support to be effective for up to 8 weeks after embryo transfer, after which time the pregnancy is self supporting.

A review of 14 randomized controlled trials (2158 women) found no evidence that routine use of progestogens can prevent miscarriages [24]. No difference in the incidence of adverse effects on either the mother or baby was apparent. There was evidence that women who have suffered three or more miscarriages may benefit from progestogen during pregnancy. Four trials showed a decrease in miscarriage compared with placebo or no treatment in these women; however, the trials were of poorer methodological quality so these findings should be interpreted with caution. The recently published robust large multicentre double blinded randomised controlled trial (PROMISE trial) [25] did not show any reduction in the miscarriage rates

or improvement in live birth rates in women who suffered from recurrent miscarriages and randomised to progesterone support or placebo in early pregnancy

In the case of threatened miscarriage, a systematic review of trials located four randomised studies involving 421 women that compared the use of progestogens in the treatment of threatened miscarriage with either placebo or no treatment [26]. The limited evidence suggests that the use of a progestogen does reduce the rate of spontaneous miscarriage. Two trials reported that treatment with progestogens did not increase the occurrence of congenital abnormalities in the newborns and the women did not have any significant difference in incidence of pregnancy-induced hypertension and antepartum haemorrhage. Further larger studies are warranted for firmer conclusions. The on-going PRISM trial is powered to definitively answer the question as to whether there is a role for progesterone in early pregnancy bleeding [27].

Heparin

The Cochrane database suggests that in antiphospholipid syndrome and recurrent miscarriage, unfractionated heparin is effective at preventing miscarriage but this was not confirmed in the one trial using low molecular weight heparin (LMWH) [28]. However, the evidence from unfractionated heparin was of such a large magnitude that it is now routine practice to give LMWH to women with antiphospholipid syndrome and recurrent miscarriage. There is a dearth of evidence as to the management of women with inherited thrombophilia with conflicting results from the published studies. The on-going multicentre randomised controlled trial (ALIFE2) [29] will shed light on the treatment of women with inherited thrombophilia especially with recurrent pregnancy loss. Peri-implantation LMWH may improve implantation in IVF but the trials are of insufficient quality to draw firm conclusions [30]. LMWH has been demonstrated to have no effect at preventing miscarriage during pregnancy in idiopathic recurrent miscarriage in several trials [31].

Aspirin

Low dose aspirin is indicated for women who are considered high risk for developing pre-eclampsia. In the United Kingdom low dose aspirin is recommended to be commenced from 12 weeks of pregnancy until labour in women at high risk of hypertensive disease in pregnancy [32]. A systematic review showed no benefit from low dose aspirin in preventing miscarriage in unexplained recurrent miscarriage. In one large randomised controlled trial there was a lower live birth rate in women with unexplained recurrent miscarriage in women taking aspirin than placebo and so should not be used for this indication [33].

Steroids

One small study suggested an improvement in pregnancy outcomes in women treated with prednisolone with raised uterine natural killer cells and recurrent miscarriage [34]. Prednisolone in early pregnancy has been associated with gestational diabetes, preterm birth. Until large randomised controlled trails have established the efficacy of prednisolone, its use as a treatment option remains in research settings only.

Immunotherapy

The immune mechanisms of recurrent implantation failure and recurrent pregnancy loss postulate the rejection of the embryo by the mother. Injection of paternal leucocytes in early pregnancy was done initially to overcome the postulated rejection phenomenon. Intravenous immunoglobulin has been subject to a series of randomised controlled trials and has potential side effects including anaphylaxis. Paternal cell immunization, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in improving the live birth rate. TNF-Alpha use is associated with severe reactions such as immunosuppression and granulomatous disease.

However, current meta-analysis of evidence has shown no benefits from the immunotherapy approaches in preventing miscarriage [35].

Use of Granulocyte Colony Stimulating Factor (G-CSF)

Has shown promising results from the use in women with recurrent implantation failure; persistent thin endometrium and recurrent miscarriage [36]. However, there have been no published randomised control trial evidence and therefore there is currently no role in early pregnancy support.

Use of Human Chorionic Gonadotropin

Improved pregnancy outcomes in women with oligomenorrhoea and suspected luteal phase deficiency have been reported [37] but the studies are not large enough to support the routine use of HCG for pregnancy support, outside of a research setting. A Cochrane review of HCG in recurrent miscarriage included five studies (involving 596 women) and suggested a statistically significant reduction in miscarriage rate using HCG. The number of women needed to treat to prevent subsequent

pregnancy loss was seven. However, when two studies of weaker methodological quality were removed, there was no longer a statistically significant benefit (risk ratio 0.74; 95 % confidence interval 0.44–1.23). There were no documented adverse effects of using HCG. The evidence supporting HCG supplementation to prevent RM remains equivocal. A well-designed randomised controlled trial of adequate power and methodological quality is required to determine whether HCG is beneficial in RM [38].

A Cochrane review of HCG for threatened miscarriage included three trials (with a total of 312 participants), found no evidence that HCG is effective as treatment for threatened miscarriage. There was no report on adverse effects of HCG on the mother or baby. More good-quality research is needed to study the impact of HCG on miscarriage [39].

Ultrasound in Early Pregnancy for Reassurance

The waiting period between the embryo transfer and pregnancy test is a period of uncertainty and anxiety and is stressful for the couple. The evidence for supportive care is predominantly from the management of women with recurrent miscarriage and pregnancy loss. Women who undergo ART experience emotional, physical and physiological stress associated with the burden of expectations and the impending fear of failure and anxiety surrounding the outcomes. This heightened sense of anxiety is worse during the waiting time between embryo transfer and pregnancy test.

The IVF protocol of units will accommodate a viability scan for all patients who underwent embryo transfer between 6 and 7 weeks of gestation. The positive information given is important and begins with a pregnancy test signalling the implantation and possible selective selection of an embryo. The ultrasound identification of an intra uterine pregnancy rules out ectopic sites of implantation. The ultrasound identification of the presence of cardiac activity adds additional reassurance as the risk of miscarriage falls significantly to 9 % at 6 weeks and further down to 0.5 % at 9 weeks. Further pregnancy care and scan will be arranged as offered routinely for any pregnancy.

While this approach is suitable for most patients, the expectations of patients with previous repeated failed IVF cycles or previous pregnancy loss would be for earlier access to ultrasound assessment of pregnancy and repeated reassurance scans. Musters et al, who conducted a qualitative research study examining the supportive care options for women who suffered from recurrent pregnancy loss, further confirmed this [1]. This was an explorative semi-structured in depth interview of 20 different options that were presented to the 17 participating women. Data were published from the interviews of 15 women excluding the two pilot study entrants. Sixteen options were preferred for the next pregnancy and four options were rejected. Examples of the preferred supportive care were early and frequently repeated ultrasounds, βHCG monitoring, practical advice concerning life style and diet, emotional support in the form of counselling, a clear formulated plan including

medications for the upcoming 12 weeks of pregnancy. Though the women acknowledged the heightened anxiety in the lead up to the scans, they still wanted the scans for reassurance and certainty that the pregnancy was ongoing.

The setting for the delivery of such services would be in a specialist clinic such as early pregnancy unit or recurrent miscarriage clinics, which are generally staffed by permanent team members. This would ensure continuity of care for the patients, familiarity with the team and the patient preference of avoiding meeting and recounting the history to several clinicians. This helps the patient and partner to build rapport with the clinician, adhere to advice, and have an agreed discussion based on the expectations with the individual couple. The setting should ideally have published protocols and adherence to the emerging evidence. Practise and outcomes should be monitored regularly against the guidelines. The research evidence must be updated and the management changed accordingly when new evidence emerges as the field is moving quickly.

Li recommends having a specialist clinic for a population of two million to adequately counsel, manage and support couples using the early pregnancy clinic service [2]. Dedicated specialist clinics should reduce the variation of practise among the clinicians and reduce the widespread use of empirical unproven treatments. The published evidence from the recurrent miscarriage/one stop clinics suggests that the scans can be offered fortnightly from 6 weeks until 12 weeks [3, 4]. Further scans can be offered for on-going support based on the anxiety of the individual patient. The one stop clinic set up in Leicester [5] significantly reduced the waiting times to access a specialist with reported live birth rate of around 67 % in women who have previously suffered from three or more miscarriages. This was possibly due to the extensive work up by investigations and tailored treatment along with supportive care.

Supportive Care

Women are routinely offered an early pregnancy scan at the fertility clinic where they are having ART. For women, who have had recurrent pregnancy losses or adverse reproductive outcome, a tailored approach is suggested to offer women support, advice and reassurance ultrasound in a dedicated setting such as Early pregnancy unit or Recurrent miscarriage clinic with a multi disciplinary team of doctors, midwives, nurses and/or psychologists.

Women who suffer from negative reproductive outcomes suffer from guilt, depression, anxiety, and psychological trauma similar to bereavement. Patients undergoing treatment for subfertility and patients with recurrent miscarriage suffer the most. There is widespread published evidence supporting the distress suffered by women with failed outcomes. 1:5 women who experience miscarriage have anxiety levels similar to people attending the psychiatric outpatient services. One-third of the women attending specialist clinics as a result of miscarriage are clinically depressed [40].

A small prospective study of 45 women evaluating the psychological component of pregnancy loss was done after two first trimester miscarriages, with other causes eliminated. Self report questionnaires and interviews before their next pregnancy showed that ten pregnancies (22.2 %) resulted in a miscarriage. The degree of baseline depressive symptoms predicted the rate of miscarriage [41]. Recurrent pregnancy loss patients are prone to heightened anger, depression, anxiety and feelings of guilt and grief.

A study from Japan showed statistically significant higher scores of mental distress as assessed by the Kesler score in women with recurrent unexplained pregnancy loss. The study acknowledged that the significance of mental state and the cardiovascular risk factors in women with unexplained recurrent pregnancy loss needs to be clarified [42]. Kolte et al. also encountered indices suggestive of high levels of stress on the PSS (perceived stress scale) among women who attended their specialist clinic [43]. Feelings of guilt and self-blame typical of depressive disorders, were highly prevalent in women with recurrent pregnancy loss. Whilst patients scored high on the MDI (Major Depressive Inventory) there was no association with lower chance of on-going pregnancy and live birth rate. A successful outcome lowered the scores in a follow up assessment. This study is useful to counsel women regarding the emotional affects of negative reproductive outcomes but can be reassured that they do not adversely affect the future pregnancy outcomes [44].

Treatment for subfertility and pregnancy loss places huge stress and strain in the marital relationship. This is due to the differing methods of coping mechanisms adopted by men and women. This can sometimes lead to the woman feeling isolated with lack of acknowledgement. Hence any support or therapy should ideally be directed to the couple rather than just the woman. Men usually feel that they are not spoken to or in the periphery of the decision making process. The acknowledgement and support from friends and family contributes positively to the emotional wellbeing of the pregnant mother. A clinical nurse with training in counselling skills or a professional psychologist can offer counselling. The women in the study by Kolte et al. rejected the option of counselling by their family doctor. Acknowledgement of the anxiety and support by the caring clinician helps women cope with the pregnancy and the outcomes even if negative.

The evidence for the use and efficacy of supportive care in early pregnancy is derived from management of patients with recurrent miscarriage or pregnancy loss. The earliest evidence is from Pedersen and Pedersen 1984 who managed women with unexplained recurrent pregnancy loss [6]. In the 85 women with the diagnosis there were 61 conceptions that were either assigned to tailored supportive antenatal care or no specific care. The outcomes in the two groups were statistically significantly different. Whilst 86 % of the pregnancies in the supportive group reached term gestation in the supportive group, the outcomes in the other group of patients was 67 % (p value <0.001). Though the study was offered to only patients who lived close to the hospital it nevertheless paved way for more studies to evaluate the novel concept of supportive care in pregnancy. A subsequent study by Clifford et al. from UK confirmed that the rates of miscarriage was significantly lower in women who attended the early pregnancy clinic at 26 % vs. the 51 % repeat miscarriage in

women who did not attend the specialist clinic [7]. The exact mechanism by which supportive care improves outcomes is not understood. Not all women with the supportive care package will have a successful outcome. However, the support that they received in the pregnancy will equip them to face and prepare for the pregnancy with confidence.

The evidence for the supportive care comes from the participation of Caucasian women in the developed countries. The participation and representation of ethnic minority women and as a couple should be encouraged. The small number of ethnic minority women in the study by Musters et al. chose a different set of options to the native Dutch women. The limited evidence suggests that they are less likely to depend on family members and peer group support and would rely on the support and treatment from clinicians [1].

Research Participation

Management of women in dedicated clinics provides the opportunity for women to participate in clinical trials to guide evidence-based management. There is still ambiguity and variation in the management of early pregnancy issues. The study by Musters et al. from the Netherlands also reported the willingness of women to participate in scientific research. The reasons behind the participation were twofold-contribution to the greater good and personal gains for themselves [1]. The Miscarriage Association Patient Information Leaflet acknowledges that taking part in a clinical trial can be helpful, even if the treatment does not turn out to be effective. It states that "patients taking part in the trial tend to get additional care and monitoring and there is some evidence that enhanced care can have a positive impact in reducing miscarriage rates." A review by Tang and Quenby concluded that women should be encouraged to participate in studies with robust questions and methodology so as to optimise investigations and treatment modalities [45]. Li et al. discuss the difficulties surrounding the set up, planning and statistical considerations required in research studies involving a sensitive and multifactorial early pregnancy issue such as recurrent miscarriage [2]. There is a current feasibility study to assess the efficacy of PCRI (Positive Reinforcement and Coping Intervention) for women who are in the waiting period of their next pregnancy. The PRCI is a novel self-administered supportive technique, which has been shown to be effective in patients awaiting the outcome of in vitro fertilisation treatment [46].

Conclusion

Early pregnancy care to women undergoing ART should be tailored specific to her pregnancy. While progesterone luteal support following IVF, heparin in acquired thrombophilia, and thyroxin in hypothyroidism are proven to be the beneficial

pharmacological interventions, most of the other interventions commonly employed to support early pregnancy are not evidence based and are to be tested in robust randomised controlled trials. Women and couples undergoing ART experience emotional, physical and physiological stress associated with the burden of expectations and the impending fear of failure and anxiety surrounding the outcomes. Ultrasound and supportive care along with provision of counselling service in a specialist clinic offers the best choice for these patients.

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