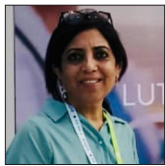


Review Article

An assisted reproductive technology workup for the couple

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ABSTRACT

Advancements in assisted reproduction technology (ART) have increased the success rates for a healthy and safe pregnancy. But after each cycle, broadly up to 50% of patients do not conceive despite having good embryos and a good endometrium. This may occur once, twice, thrice, and so on. The question then comes, do we need to do anything extra regarding investigations and treatment to translate it into success, or is it just chance, or is it something we do not yet have evidence for? Guidelines on recurrent implantation failure (RIF) emphasize certain RIF-specific investigations as recommended and those that can be considered. Recent studies have highlighted a >95% clinical pregnancy rate after up to three/five consecutive euploid blastocyst transfers. Further, where data were available, the implantation rate of the fourth euploid blastocyst transfer was similar to the first transfer. This emphasizes that all modifiable factors need to be investigated at the upfront, rather than having a tiered approach. Essentially, then, a pre-ART workup would include lifestyle factors, genetic counseling, and investigations for the couple. For the female partner, an endocrinology workup, identifying a normal uterine and adnexal anatomy by transvaginal ultrasound, 3D ultrasound, sonosaline salpingography, and/or hysteroscopy. Recent literature supports screening hysteroscopy as a pre *in vitro* fertilization workup. Chronic endometritis diagnosis and its treatment with antibiotics is recommended as an intervention in RIF patients. Hysteroscopy is the gold standard for diagnosing chronic endometritis. For the male partner, semen analysis, and as indicated, an endocrinology and imaging workup. Specifically for patients with severe oligospermia/non-obstructive azoospermia, a karyotype and Y chromosome microdeletion as indicated. DNA fragmentation tests are recommended for patients with a history of abortions in the female partner. Options for expanded carrier screening can be discussed with the couple, considering that 2–4% of reproductive couples are at risk of having a child with an autosomal recessive or X-linked genetic disorder. The pre-ART workup needs to be discussed with the couple regarding the benefits, evidence, and cost. The final decision is with the couple to opt for the investigations as a tiered approach or upfront before the first cycle.

Keywords: Couple, Pre-assisted reproduction technology, Pre *in vitro* fertilization, Workup

AN ASSISTED REPRODUCTIVE TECHNOLOGY WORKUP FOR THE COUPLE

A systematic workup before assisted reproduction is essential for the couple, not only for improving the success rates but also for a safe and healthy pregnancy. The whole *in vitro* fertilization (IVF) process is a mental, physical, and financial stress for the couple. Modifiable factors related to the success of IVF need to be identified beforehand.

The European Society of Human Reproduction and Embryology's good practice recommendations on recurrent implantation failure (RIF) give a tiered approach of investigating the couple, enlisting specific tests to be performed in these couples.^[1] Pirtea *et al.* emphasized

that true recurrent implantation is <5%.^[2] The sustained implantation rates were comparable in the first three euploid blastocyst transfers. These data were further expanded by Gill *et al.*^[3] The cumulative live birth rate (LBR) after five euploid blastocyst transfers was 98.1%. The pre-conception evaluation included all obvious maternal causes for implantation failure, such as communicating hydrosalpinx, uterine intracavitary pathology, congenital uterine anomalies, adenomyosis, obesity, and parental karyotype abnormality.^[3] These studies highlight that there is no dramatic reduction in the implantation rates with each successive transfer.^[2-4] This does not support the notion that there is an inherent endometrial pathology in these patients leading to implantation failure, provided the uterus is anatomically normal as determined by saline sonography and/or hysteroscopy with a euploid blastocyst transfer in an artificial cycle with endometrial thickness ≥ 7 mm and with intramuscular progesterone as luteal phase support.^[2] This emphasizes the significance of the pre-IVF workup of couples at the upfront to manage the modifiable factors rather than a tiered approach [Table 1].^[5]

In this review, we will expand on the pre-IVF workup of the couple, emphasizing the evidence-based preconception counseling, including lifestyle modifications, genetic testing, and clinically relevant investigations in each partner.

COMMON WORKUP FOR BOTH PARTNERS

The specific investigations for the female partner and specific investigations for the male partner in the same size and font as Common workup for both partners.

PRE CONCEPTION COUNSELING

1. Lifestyle factors, including weight, physical activity, dietary patterns, caffeine, alcohol, smoking, vitamins, antioxidants, recreational drugs, and stress
2. Infectious disease screening
3. Environmental pollutants
4. Vaccinations
5. Occupational hazards.

LIFESTYLE FACTORS

Weight, physical activity, and dietary patterns

For the female partner

There is evidence regarding both over- and underweight disorders impairing fertility.^[6] The general evidence points to overweight (body mass index [BMI] >25 kg/m²) and obesity (BMI >30 kg/m²) negatively affecting assisted reproduction technology (ART) outcomes.^[7-9]

Physical activity improves hormone profile and reproductive function.^[7] Guidelines suggest women planning to conceive gradually increase their physical activity to 10,000 steps a day and/or engage in moderate aerobic exercise 150 min/week.^[9,10]

Most of the studies showed a positive correlation between a Mediterranean diet (high in omega-3 fatty acids, some antioxidants, vitamins, and low in saturated and trans fatty acids) and pro-fertility diets with better reproductive outcomes [Table 2].^[11,12]

For the male partner

Obesity can negatively affect ART outcomes, especially when accompanied by metabolic syndrome.^[13]

The guidelines recommend regular resistance and/or high-intensity exercise in sedentary, infertile males with abnormal semen parameters to improve pregnancy rates.^[14,15]

In men, the Mediterranean diet is related to improved semen parameters as it is a diet with antioxidant and anti-inflammatory effects [Table 1].^[16]

Caffeine

Though a safe level is not defined, it is recommended to keep this below 200 mg/day.^[17,18]

Alcohol

There are clear adverse effects on fertility and pregnancy, a higher risk of miscarriage, and adverse effects on fetal development in women with alcohol consumption.^[8] Limiting to 1–2 units/week or consuming no alcohol is recommended.^[8] Moderate alcohol (<6 units/week) does not adversely affect semen parameters, while high alcohol intake can have a detrimental effect on male fertility and LBRs.^[8,16]

Smoking

It is associated with a dose-dependent effect. Active female smokers and non-smoking women with smoking partners/environment have a negative effect on IVF outcomes to the extent that smoking women need twice the number of IVF cycles to conceive compared to non-smokers.^[8] In men, low-quality evidence exists to link smoking with poorer semen parameters and increased oxidative stress.^[14,19,20]

Vitamin D

Vitamin D assessment and supplementation are common, the evidence for its benefit in ART is controversial.^[1,21-23] Despite this, vitamin D assessment and supplementation are widely used in clinical practice.^[1,21]

Table 1: Recommendations for preconceptional counseling for couples undergoing ART- Lifestyle factors.

Society Guidelines	Recommendation
EUA Guidelines on sexual and reproductive health 2024 ^[19] <ul style="list-style-type: none"> In infertile men, lifestyle factors including obesity, low physical activity, smoking and high alcohol intake are associated with decreased sperm quality. Advise men to improve lifestyle factors to improve chances of conception. 	Strong recommendation
AUA/ASRM Guidelines Diagnosis and treatment of infertility in men 2020; Amended 2024 ^[14] <ul style="list-style-type: none"> Clinicians may discuss risk factors (<i>i.e.</i>, lifestyle, medication usage, environmental exposures, occupational exposures) associated with male infertility, and counsel the patients that the current data on the majority of risk factors are limited. 	Conditional recommendation
ACOG Committee Opinion Prepregnancy counseling 2019 ^[10] <ul style="list-style-type: none"> Exercise 30 min a day/5 days a week/150 min a week BMI (18.5 kg/m²–30 kg/m²) Stop smoking / effective strategies for tobacco cessation Patients were counseled that there is no safe level or type of alcohol use Discontinue recreational drugs 	
ESHRE Task force on lifestyle-related factors and access to medically assisted reproduction 2010 ^[8] <ul style="list-style-type: none"> BMI <30 kg/m² Smoking associated with dose-dependent compromised reproductive outcomes, also for non-smoking women with a smoking partner/environment Alcohol affects reproductive outcomes in a dose-dependent way. Reduced conceptions reported even with as low as one drink per week 	
ESHRE Good practice recommendations on recurrent implantation failure 2023 ^[1] <ul style="list-style-type: none"> Reassessment of lifestyle factors and their optimization 	Recommended
ESHRE Guidelines: Psychosocial care in infertility and medical assisted reproduction 2015 ^[29] <ul style="list-style-type: none"> Give information about lifestyle behaviors that may negatively affect patients' reproductive health 	Good Practice Point
ART: Assisted reproductive technology, EUA: European Association of Urology, AUA: American Urological Association, ASRM: American Society for Reproductive Medicine, ACOG: American College of Obstetricians and Gynecologists, ESHRE: European Society of Human Reproduction and Embryology, BMI: Body mass index	

Male antioxidant

Infertile men are frequently associated with oxidative stress, but the overall quality of evidence is low for the use of antioxidants. The guidelines do not routinely recommend antioxidants for male infertility.^[19]

Recreational drugs

Includes cocaine, cannabis, and methamphetamines. Cannabis used in either partner impairs fertility and reproductive outcomes.^[24,25] Cocaine alters ovarian responsiveness and compromises sperm function.^[26] Ongoing use of anabolic steroids can interfere with infertility.^[14]

Stress

Anticipatory anxiety stress is increased in infertile couples.^[27,28] Guidelines are recommended for routine psychosocial care at infertility and medically associated reproduction clinics.^[29]

INFECTIOUS DISEASE SCREENING

Infections of the reproductive tract can alter immune and inflammatory responses and reduce fertility. Couples should

be screened and treated for any infection of the reproductive tract. A cervical cytology and human papillomavirus testing according to the guidelines needs to be done. Syphilis and viral markers need to be evaluated for hepatitis B, C, and human immunodeficiency viruses.^[10,30]

ENVIRONMENTAL POLLUTANTS

These environmental pollutants are often referred to as endocrine-disrupting chemicals, which can interfere with normal reproductive outcomes.^[31-33] A precautionary approach is recommended, including good hygiene practices, washing fruits and vegetables, and limiting exposure to outdoor and indoor chemicals.^[16]

VACCINATIONS

Due to the consequences of being infected with rubella, varicella zoster, and influenza in pregnancy, immunization before pregnancy, as appropriate, is advised.^[34]

OCCUPATIONAL FACTORS

Dysregulation of circadian rhythms associated with shift work contributes to menstrual cycle irregularity, altered follicle-stimulating hormone (FSH) levels, and poor reproductive outcomes.^[35,36]

GENETIC WORKUP

Couple karyotype

Prevalence of chromosomal abnormalities in infertile couples for ART is 2.8–12% in males and 3–5% in females.^[37] The incidence of balanced translocation is upto 1.1% for infertile couples, up to 5% for recurrent pregnancy loss, and upto 9% in couples with more than 3 first-trimester pregnancy losses.^[38-40] In case of the previous birth of a child with congenital abnormalities, offspring with an unbalanced chromosomal abnormality in the family, or detection of a translocation in a previous abortion, a couple's karyotype is recommended.^[41] A couple's karyotype is also recommended in RIF [Table 2].^[1]

Carrier screening

The American College of Obstetricians and Gynecologists recommends informing and counseling all patients planning a pregnancy regarding genetic carrier screening.^[42] Individuals with a positive family history of a genetic condition should be offered carrier screening for that particular condition. Specific conditions recommended are hemoglobinopathies, spinal muscular dystrophy, and cystic fibrosis. Fragile X syndrome gene testing is recommended

for women with a family history of fragile X-related disorders.^[10,42] The options of preimplantation genetic testing for monogenic disorders (PGT-M) and PGT for structural rearrangements (PGT) are to be discussed with the couple in case of a single-gene defect in the family/partners and the presence of a balanced translocation in either partner, respectively [Table 2].

Expanded carrier screening (ECS)

It is estimated that about 2–4% of reproductive couples are at an increased risk of conceiving a child with an autosomal recessive or X-linked disorder.^[43,44] Though there is no ideal threshold to determine which diseases to include in the ECS panel, diseases with a well-defined phenotype and a detrimental effect on quality of life with a carrier frequency of 1:100 are a useful threshold.^[45] The challenges with ECS revolve around the content, variant classification, counseling, and cost of the test [Table 2].

Specific indications for genetic tests of the female partner

Chromosomal analysis is recommended to be done in patients with primary amenorrhea or premature ovarian insufficiency (POI).^[46] Chromosomal abnormalities are

Table 2: An assisted reproductive technology genetic workup for the couple.

Investigation	Female partner	Evidence	Male partner	Evidence
Karyotype	Primary amenorrhea POI	ESHRE/ASRM Guidelines 2024 ^[46] Strong recommendation	<ul style="list-style-type: none"> Azoospermia <5×10⁶ per mL with elevated FSH/testicular atrophy/ impaired sperm production RPL 	AUA/ASRM Guidelines 2020 ^[14] Expert opinion EUA Guidelines 2024 ^[19] Strong recommendation AUA/ASRM 2020 ^[14] Expert opinion
Couple Karyotype	<ul style="list-style-type: none"> Previous child with a congenital abnormality Offspring with an unbalanced chromosomal abnormality in the family Detection of translocation in pregnancy tissue RIF 		<ul style="list-style-type: none"> ESHRE Guidelines 2022^[41] Conditional recommendation ESHRE Good practice recommendations 2023^[1] can be considered 	
Carrier Screening	<ul style="list-style-type: none"> Spinal muscular atrophy Cystic fibrosis Haemoglobinopathies (Haemoglobin electrophoresis) Fragile X premutation Family history of fragile X-related disorders POI 	ACOG Committee opinion 2017 ^[42] ESHRE/ASRM Guidelines 2024 ^[46] Strong recommendation		
Expanded carrier screening	<ul style="list-style-type: none"> It should be introduced as an option to the couple Preferably limited to recessive, serious congenital and childhood disorders and to class 4/5 variants linked with these diseases 			ACOG Committee opinion 2017 ^[45]

RPL: Recurrent pregnancy loss, RIF: Recurrent implantation failure, POI: Premature ovarian insufficiency, ESHRE: European Society of Human Reproduction and Embryology, ASRM: American Society for Reproductive Medicine, AUA: American Urological Association, EUA: European Association of Urology, ACOG: American College of Obstetricians and Gynecologists

seen in 50% of patients with primary amenorrhea and 10–13% patients with POI.^[46-48] Fragile X syndrome testing is indicated in all women diagnosed with POI.^[46]

Specific indications for genetic tests of the male partner

For the male partner, atleast 15% of the male infertility can be explained by genetics.^[49] The frequency of chromosomal abnormalities increases with the severity of oligospermia and with non-obstructive azoospermia (NOA). Patients with a sperm count <5 million per mL have a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities. Men with NOA are at the highest risk, especially for sex chromosomal anomalies. There is a strong recommendation in the guidelines to offer karyotype analysis and genetic counseling to all men with azoospermia and a semen count <5 million/mL.^[19] Y chromosome microdeletion testing is recommended for sperm concentration ≤1 million/mL and in cases of NOA.^[14,19] It can also be considered in men with a sperm count <5 million/mL.^[19] There is a strong recommendation to test men with structural abnormalities of the vas deferens (unilateral or bilateral absence with/without renal anomalies) for cystic fibrosis transmembrane conductance regulator gene mutations, and if found to be a carrier, then to test the partner also.^[14,19]

FEMALE PARTNER SPECIFIC WORKUP

History-taking includes menstrual history, previous pregnancies and outcomes, family/personal history of genetic diseases, previous fertility treatment, pelvic surgeries,

pelvic diseases, history of endocrine/chronic diseases, and a general health and systematic examination of the patient. An endocrinology workup for thyroid function, thyroid antibodies, and prolactin is required.^[50] If suspecting polycystic ovary syndrome/hirsutism, an endocrine workup is performed accordingly.^[21] If there is a history of abortions, screening for acquired thrombophilias, antiphospholipid antibody syndrome, and antinuclear antibodies is recommended.^[41,51] Ovarian reserve markers, antimüllerian hormone, antral follicle count, day 2 FSH, luteinizing hormone, and estradiol levels also need to be estimated.^[21,52] Transvaginal ultrasound (TVUS) for uterine anatomy, endometrium, adenomyosis, uterine cysts, isthmocol, adenexa, hydrosalpinx, and endometriosis is recommended.^[4,5,21,53-59] There is limited evidence to include an endometrial biopsy for histopathology and diagnosing endometritis in the workup.^[60] In patients where the plan is to do a natural cycle frozen embryo transfer (ET), assessment of mid-luteal progesterone may be considered to assess the corpus luteum function.^[61,62] Late follicular/mid-luteal progesterone levels should be considered in patients with RIF [Table 3].^[1]

Uterine cavity evaluation

TVUS 2-dimensional (2D)

It is the first-line diagnostic tool. Its sensitivity to detect intrauterine abnormalities ranges from 56% to 89% with a specificity of 53–100%.^[63]

History	• Medical/reproductive/family.
Examination	• GPE/gynecological evaluation (thyroid/breast/pelvic examination)
Endocrine workup	• AMH/day 2 FSH/LH/E2 (autologous oocytes) • Thyroid function test • Prolactin (if symptomatic) • PCOS-specific workup (if clinically indicated) • Hirsutism-Specific workup (if clinically indicated) • Late follicular/mid-luteal progesterone levels
APA/APS	• Assessment recommended with/or without risk factors in patients with RIF
TVS 2D	• For all patients
Uterine cavity assessment	• TVUS 3D • If not available SIS/MRI • Hysteroscopy to confirm and treat the uterine cavity assessment • Screening hysteroscopy-limited evidence. • Hysteroscopy and chronic endometritis testing can be considered in RIF
Hydrosalpinx	• If suspected on TVUS 2D: Confirm by HSG/Hysterosonography
Mock embryo transfer trial	• Universal use- contradictory evidence
GPE: General physical examination, AMH: antimüllerian hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, PCOS: Polycystic ovary syndrome, APA: Antiphospholipid antibodies, APS: Antiphospholipid syndrome, RIF: Recurrent implantation failure, TVUS 3D: Transvaginal ultrasound 3 dimensional, SIS: Saline infusion sonography, MRI: Magnetic resonance imaging, HSG: Hysterosalpingography	

TVUS 3D

It is as effective as magnetic resonance imaging for diagnosing uterine malformations. It is comparable to hysteroscopy for diagnosing intrauterine lesions.

Saline infusion sonohysterography (SIS)

This improves detection of intrauterine lesions from 67% to 87% as compared to TVUS.^[64] There is no significant difference in the accuracy between 2D and 3D SIS in detecting uterine cavity lesions.^[65]

Hysterosalpingography (HSG)

It delineates the uterine cavity but has a high false-positive and false-negative result.

Hysteroscopy

This remains the gold standard for diagnosing intrauterine lesions. It is specifically indicated for further evaluation and treatment of suspected uterine anomalies, in cases of altered endometrial pattern, irregular spotting, high risk for endometritis, fluid in the endometrial cavity on TVUS, with limited evidence for screening hysteroscopy.^[66-68]

Screening hysteroscopy

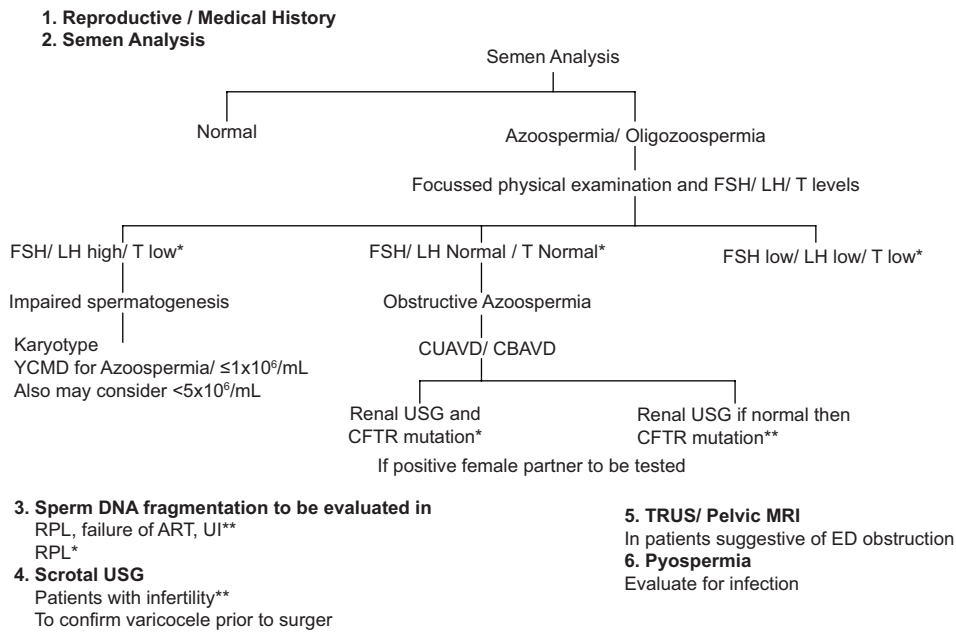
A recent systematic review and meta-analysis observed an increase in clinical pregnancy rates when hysteroscopy was offered before the first IVF cycle.^[66] A further updated review also highlights the pivotal role of hysteroscopy in diagnosing and treating subtle uterine lesions, improving reproductive outcomes.^[67] Emerging evidence points to the diagnosis and treatment of chronic endometritis before IVF for better reproductive outcomes.^[69,70] In RIF, hysteroscopy and assessment for the diagnosis of chronic endometritis can be considered.^[1]

ENDOMETRIAL MICROBIOME

Evidence for the effect of the upper tract microbiota on reproductive outcomes is not outlined.^[1] It may be responsible for infertility, or it could be a marker for some other causative factor.^[71-73] Relevant areas that need to be addressed are the optimal means of testing, when to test, the stability of a particular microbiome, relation to menstrual cycle, sexual activity, and IVF treatment.

EVALUATION FOR HYDROSALPINX

The presence of hydrosalpinx before ET lowers the success rate of pregnancy.^[74] If hydrosalpinx is suspected on TVUS,



*Reference 14, ** Reference 19

Abbreviations: ART: Assisted Reproductive Technology, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, T: Testosterone, YCMD: Y chromosome microdeletion, CUAVD: Congenital Unilateral Absence of Vas Deferens, CBAVD: Congenital Bilateral Absence of Vas Deferens, USG: Ultrasound, CFTR: Cystic Fibrosis Transmembrane Conductance Regulator, DNA: Deoxyribonucleic Acid, RPL: Recurrent Pregnancy Loss, UI: Unexplained infertility, AUA: American Urology Association, ASRM: American Society for Reproductive Medicine, TRUS: Transrectal Ultrasound, MRI: Magnetic Resonance Imaging, ED: Ejaculatory Duct

Figure 1: Pre-assisted reproduction technology male partner workup.

it can be confirmed by HSG/SIS/Hysterosalpingo contrast sonography, though contrast instillation may increase the risk of infection.^[75] In case tubal pathology is not suspected on TVUS, further tests to diagnose hydrosalpinx are not recommended.^[74]

MOCK ET

Mock ET can identify cases where a difficult ET would be expected.^[76] Studies related to the benefit of a trial transfer are limited, with contradictory results.^[77] A recent study highlights a non-invasive screening tool based on ultrasound findings of the cervical canal, the cervical position, and a history of cesarean section without a vaginal delivery for predicting a difficult ET.^[76]

MALE PARTNER SPECIFIC WORKUP

A general and genitourinary examination, along with semen examination, at the outset.^[19] An endocrinology workup is required in case of abnormal semen analysis.^[14,19,21,78] Imaging needs to be done in cases of azoospermia, oligospermia, and varicocele.^[14,19,21] Sperm DNA fragmentation may be associated with poor outcomes and recurrent pregnancy loss.^[14] It is recommended for patients with a history of recurrent pregnancy loss, a previous unsuccessful ART cycle, and unexplained infertility [Figure 1].^[14,19]

CONCLUSION

Meticulous planning and workup are required before ART to maximize the success rates and to optimize the obstetric outcomes for a safe pregnancy and healthy baby. The workup can be stratified into a basic evidence-based essential workup before the first IVF cycle. Second tier of tests, which are evidence-based for patients of RIF, specifically genetic counseling/testing, 3D ultrasound/hysteroscopy, and diagnosing chronic endometritis, can be offered to the couple at the outset. All modifiable factors that can lead to failed implantation need to be identified and managed along with lifestyle issues to maximize the success rates of the first IVF cycle. The planning should be non-directive, respecting the couple's autonomy in decision-making. The final decision is with the couple after discussing the evidence, benefits, and costs.

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