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Infertility and Perinatal Loss: When the Bough Breaks

Amritha Bhat¹ and Nancy Byatt²

Amritha Bhat: amritha@uw.edu

¹Department of Psychiatry, University of Washington, Box 35650, Seattle, WA 98195, USA

²Departments of Psychiatry and Obstetrics and Gynecology, UMass Medical School, Worcester, MA, USA

Abstract

Infertility and perinatal loss are common, and associated with lower quality of life, marital discord, complicated grief, major depressive disorder, anxiety disorders, and posttraumatic stress disorder. Young women, who lack social supports, have experienced recurrent pregnancy loss or a history of trauma and / or preexisting psychiatric illness are at a higher risk of experiencing psychiatric illnesses or symptoms after a perinatal loss or during infertility. It is especially important to detect, assess, and treat depression, anxiety, or other psychiatric symptoms because infertility or perinatal loss may be caused or perpetuated by such symptoms. Screening, psychoeducation, provision of resources and referrals, and an opportunity to discuss their loss and plan for future pregnancies can facilitate addressing mental health concerns that arise. Women at risk of or who are currently experiencing psychiatric symptoms should receive a comprehensive treatment plan that includes the following: (1) proactive clinical monitoring, (2) evidence-based approaches to psychotherapy, and (3) discussion of risks, benefits, and alternatives of medication treatment during preconception and pregnancy.

Keywords

Infertility; Perinatal loss; Depression; Anxiety

Introduction

Conception, pregnancy, and childbirth are critical transitions for women. Infertility and perinatal loss, referred to together as reproductive trauma, can change a woman's perception of herself, and be a major source of stress that often has psychological consequences. Reproductive trauma occurs in up to 15 % of woman and is often associated with psychiatric symptoms or disorders. Not only can reproductive trauma lead to grief, depression, anxiety and post-traumatic stress disorder (PTSD), these psychiatric symptoms themselves have also been associated with infertility and miscarriage. In this paper, we summarize recent studies

Correspondence to: Amritha Bhat, amritha@uw.edu.

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and reviews examining psychiatric aspects of infertility and perinatal loss and provide recommendations for detection and management.

Methods

MEDLINE/PubMed was searched for the period up to September 2015 for English-language studies using the following key terms: infertility, miscarriage, abortion, stillbirth, neonatal death in association with grief, depression, anxiety, and post-traumatic stress disorder (PTSD). All articles were cross-referenced. Open and randomized controlled trials, original observational studies, case reports, case series, and reviews were included.

Infertility

Definitions and Epidemiology

Infertility is defined as 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycle [1]. While 9 to 15 % of the childbearing population experience infertility, only about half seek infertility treatment [2].

Psychological Distress as a Cause of Infertility

While the field is slowly phasing out the term “psychogenic infertility” wherein all medically unexplained infertility is attributed to psychological causes [3, 4], many women with infertility believe that the emotional distress they experience contributes to their continued infertility. Mechanisms by which depression, anxiety, and emotional distress can contribute to infertility include HPA axis dysregulation [5•], GnRH pulse inhibition [6], and autonomic nervous system activation [7]. Secondary effects of depression and anxiety on overall health and nutrition may also contribute to infertility. In addition, depression may reduce women’s motivation to continue with fertility treatments after failed treatments. Unfortunately, the evidence examining the relationship between infertility and depression or anxiety is inconclusive. While one meta-analysis found that stress and anxiety were associated with lower clinical pregnancy rates among women undergoing infertility treatment [8], another meta-analysis found no such association [9]. A large prospective study of women undergoing their first in vitro fertilization (IVF) treatment found that successful pregnancy rates were similar among women with or without psychiatric symptoms or diagnoses [10]. However, these findings cannot be generalized to untreated populations or women who receive less invasive treatment.

Psychological Distress as a Consequence of Infertility

Emotional responses to infertility include infertility-specific stress, and anxiety and depressive symptoms and disorders. Distress, loss of control, social isolation, low self-esteem, and stigma are all common responses; distress may last as long as 20 years after unsuccessful infertility treatment [11]. Most studies examining this issue are limited because they are cross-sectional studies conducted in infertility clinics, and couples seeking treatment for infertility generally have higher levels of distress or a longer duration of infertility. In fact, infertility treatments may be associated with higher levels of distress than infertility itself [12]. Infertility treatments vary in degree of invasiveness and side effect

burden (Table 1). Especially distressful is the waiting period following embryo transfer during IVF [15]. However, these findings have not been consistent, as women preparing for their first IVF treatment have also been found to have depression scores lower than local postpartum patients or general populations [16]. In addition to overall psychological distress, infertility can also lead to specific psychiatric diagnoses and symptom clusters.

Psychiatric Disorders in Women With Infertility

Rates of major depressive disorder (MDD) in women undergoing infertility treatment are as high as 17–19.5 % [17, 18] and up to 15.3 % in men [18]. Past history of MDD predicts MDD during infertility treatment among both men and women, even after controlling for other well-established risk factors (i.e., baseline levels of depression, anxiety, and partner support) [19]. For depressive symptoms not amounting to a depressive episode, risk factors include gender roles, social pressure, shame, self-judgment, acceptance, helplessness, and coping strategies [19]. Social support is protective of depression and anxiety in the context of infertility [20]. Rates of generalized anxiety disorder (GAD) in women seeking infertility treatments are also high at 23.2 % [17]. Population-based studies are conflicting. Some studies report that infertility is associated with higher depressive symptom levels [21], and others report no difference in levels of depression and anxiety among women with current infertility compared to those without [22•].

Psychological Responses During a Successful Pregnancy After Infertility Treatment

Even when assisted reproductive technology (ART) treatment results in a successful pregnancy and normal childbirth, women are vulnerable to psychological distress. Despite successful treatment, a history of infertility is associated with higher levels of pregnancy-related anxiety, lower postnatal self-confidence and early parenting difficulties [23], and an increased risk (incidence rate ratio of 2.9) of psychiatric disorders (including psychotic and affective disorders) in the first 90 days postpartum [24].

Infertility in Men

Infertility is often attributed more to the female than the male partner [25], and infertility treatment is more time consuming and painful for women than it is for men (Table 1). Hence, there is an overall impression that the psychological consequences of infertility are less severe in men than in women [26]. However, studies have found no differences in the distress levels of men and women undergoing infertility treatment [25]. For example, Fisher et al. [27] found that 84% of men diagnosed with infertility desired parenthood as much as their partners did. These findings caution against assuming that infertile men are less distressed than women about infertility. Certain factors such as social isolation may increase susceptibility to psychological distress in the context of infertility among men [28].

Impact on Relationships

The impact of infertility on relationship differs based on the stage of infertility treatment. While couples at the beginning of infertility treatment have higher relationship satisfaction compared to the general population, 5 years after starting infertility treatment, satisfaction

with the relationship declines [29]. Infertility is also associated with a negative impact on sexual desire and sexual arousal in both men and women, especially so in women [25].

Screening for Psychological Distress/Psychiatric Symptoms in the Context of Infertility

Although there are no evidence-based guidelines on screening, some IVF clinics use screening instruments such as the 34-item SCREENIVF, and women undergoing artificial reproductive technology (ART) treatments report that screening for emotional problems is acceptable and helpful [30]. SCREENIVF aims to identify women at risk for emotional maladjustment before the start of their IVF/intra cytoplasmic sperm injection (ICSI) treatment. It measures risk factors for pretreatment anxiety, pretreatment depression, helplessness regarding fertility problems, low acceptance regarding fertility problems, and lack of social support. It has a sensitivity of 69 % and a specificity of 77% [30]. Screening should be done in conjunction with a system that can ensure appropriate mental health assessment and management.

Management

Yoga [31], positive reappraisal coping intervention (PCRI; a self-administered supportive technique), and group, individual, and couple psychotherapy (psychodynamic, cognitive behavioral, or educational) can all reduce depression and anxiety among patients undergoing IVF treatment [32]. Interventions are especially effective in reducing psychiatric symptoms when provided early in the infertility treatment course [33]. Psychological interventions for infertility are important to promote both improved mental health and increased pregnancy rates. Infertile women who receive some form of psychosocial intervention are twice as likely to become pregnant as those who do not [34]. Some reports [33], but not others [35] show that pregnancy rates improve among couples receiving psychotherapy.

Women with infertility often suffer from depressive/anxiety symptoms or disorders. This presents a rare opportunity for preconception counseling that should be leveraged. Given that depression and anxiety are associated with infertility and with negative birth, infant, and child outcomes, it is important to proactively discuss the management of psychiatric symptoms during preconception. It should be emphasized that adequate treatment of depression and anxiety is a critical aspect of optimizing maternal mental health and fertility. All available treatment options including psychotherapy and pharmacotherapy should be considered and discussed with women. Up to 4.3 % of women undergoing infertility treatment are on SSRIs [36]. Providers and patients need to take into consideration and discuss the effects of both untreated illness and medication on birth, infant, and child outcomes.

Depression in pregnancy is a well-known risk factor for postpartum depression [37] and has deleterious effects on birth [38, 39, 40] and infant outcomes [41, 42]. Although some findings are conflicting [43], there is substantial evidence that discontinuation of antidepressants may increase the risk of relapse into depression [44]. This risk of relapse may be heightened during infertility treatment [5]. Although antidepressant use in pregnancy has been inconsistently associated with preterm birth, low birth weight, increased rate of congenital malformations, postnatal adaptation syndrome, and persisting pulmonary

hypertension in the newborn, recent meta-analyses have been reassuring [39, 45, 46]. It is notable that statistical significance does not necessarily imply clinical significance, and in many women, the benefit of using the medication outweighs the risk. In addition to medication treatment, evidence-based psychotherapy interventions such as interpersonal psychotherapy (IPT) or cognitive-based therapy (CBT) [47] must be maximized.

It is also important to consider and encourage social support [20], and be cognizant of the cultural variation in the psychosocial aspects of infertility. Explanatory models for infertility differ across cultures and include witchcraft and sexual promiscuity. Women may carry a disproportionate amount of blame when a couple is infertile, and there may be secondary effects of childlessness such as reduced social status [48].

In summary, infertility treatments can have various ramifications including depression and anxiety in both men and women, and emotional and sexual discord between partners. Education and support must be provided to the couples regardless of the presence of any psychiatric symptoms. Couples/individuals with clinically significant symptoms should have a comprehensive treatment plan in place that includes the following: (1) assessment and ongoing monitoring for psychiatric symptoms, (2) maximization of evidence-based interventions including cognitive behavior therapy [49] and interpersonal psychotherapy [47], and (3) an individualized risk benefit discussion and medication plan that takes into account the risk of medications and the risk of illness itself to mother, baby, and family.

Perinatal Loss

Definitions and Epidemiology

Perinatal loss is the non-voluntary end of pregnancy or death of the baby from conception until 28 days into a newborn's life. The term perinatal loss includes miscarriage, stillbirth, and neonatal death (Table 2).

Psychological Aspects of Perinatal Loss

Understanding and addressing psychological aspects of perinatal loss is critical because of the psychological reactions of women (grief, depression, anxiety, PTSD, suicide) and the impact on subsequent pregnancies and relationships with partners and surviving siblings [58, 59].

Grief

The grief that follows miscarriage often declines significantly by 6 months for both men and women, yet sometimes persists for up to 2 years [60, 61]. Perinatal loss leads to complicated grief more frequently than other losses [62]. Several factors may contribute to this. Pregnancy loss is often sudden and unexpected. The grief that parents experience after early pregnancy loss is often "disenfranchised" [63]; it is often not openly acknowledged or socially supported. Perinatal loss is associated with guilt or self-blame, and women may feel that their bodies have failed.

Predictors of complicated grief following perinatal loss include lack of social support, preloss major depression, ambivalence about pregnancy, and termination of pregnancy for

fetal anomaly. Termination of pregnancy for fetal anomaly is associated with higher levels of self-blame, guilt, and social isolation [64]. Other factors that have been reported as predictive in some, but not all studies [65], include older maternal age, having viewed an ultrasound, having experienced quickening (fetal movement), having named the baby or bought things for the baby, and length of gestation [60, 65]. Whether miscarriage is managed medically or surgically does not have a bearing on the intensity or duration of grief [66]. The presence of living children is protective against grief after perinatal loss. The perinatal loss of a co-twin or a higher order pregnancy is associated with unique challenges such as enduring the trauma of prolonged hospitalization for the surviving twin and keeping grief “on hold” to support the surviving baby [67].

Grief following perinatal loss is a normal phenomenon. Nonetheless, women, especially those with risk factors, should be monitored for prolonged or complicated grief and persistence of depression, anxiety, or posttraumatic symptoms.

Depression

It is important to distinguish grief from complicated grief and depression because there is significant overlap between the symptoms of psychiatric disorder and grief. Women who experience a perinatal loss have fourfold higher odds than women with a live birth of screening positive for depression [68•]. Risk factors for persisting depression/psychological distress after miscarriage are infertility treatment [69], recurrent pregnancy loss, prior history of depression [70], prior PTSD, intimate partner violence (IPV) [68•], and high levels of distress immediately after miscarriage [71]. There is also a higher risk of inpatient or outpatient psychiatric treatment 12 months after fetal death. The highest risk is for women with a loss occurring after 20 weeks of gestation, and the most commonly reported psychiatric disorder is adjustment disorder [72]. However, 5 to 18 years after intrauterine fetal death (IUFD), there are no significant increases in depression scores [73]. Thus, while women with recurrent miscarriages and a past history of depression and fetal death after 20 weeks of gestation are at a high risk of depression/adjustment disorder in the year following perinatal loss, this risk declines subsequently.

Anxiety

Perinatal loss is associated with an increased risk of anxiety in the first 4 months after loss [74]. Even having a living child has not been shown to protect against anxiety in women with a history of miscarriage. In longitudinal studies, this anxiety has been shown to be significantly greater than the general population at 10 days following the miscarriage, but not at 6 months, 2, or 5 years [75]. At 9 months after perinatal death (stillbirth and infant death), women with perinatal death had more than twice the odds for generalized anxiety disorder and social phobia even after adjusting for demographic factors, current depression, and past h/o psychiatric disorders [76]. Given that only 28% of bereaved mothers with anxiety symptoms access psychiatric treatment [76], it is critical that women are screened, assessed, and linked with mental health care.

Post-Traumatic Stress Disorder (PTSD)

PTSD rates are increased after all types of perinatal loss—miscarriage, termination of pregnancy, stillbirth, and neonatal death. Risk factors for PTSD include younger age, lower education, previous trauma, and mental health problems [77]. Longer gestational ages are associated with greater severity of PTSD [77]. Even 9 months after a stillbirth or neonatal death, women have a sevenfold higher rate for screen positive PTSD when compared with women with live births. It is important to encourage the use of available social support because having a support network is associated with less depression and PTSD [68].

Suicide

While the term “maternal mortality” is usually associated with obstetrical causes such as postpartum hemorrhage and pulmonary embolism, suicide also confers risk for maternal mortality. The mean annual suicide rate is higher (18.1 per 100,000) in the first year after miscarriage than after live birth (5.9) or in the general population (11.3) [78]. Registry studies have estimated a 50% increased risk of suicide in parents who lost a child between the ages of 0 and 18 [79]. Stillbirth or neonatal death has not been associated with higher maternal suicide in other studies [80].

Psychological Responses During a Subsequent Pregnancy

Although 50 to 80 % of women who experience miscarriage become pregnant again, another pregnancy is not protective against depression or anxiety [81]. There are conflicting findings with regard to the risk for perinatal depression among women with a history of miscarriage, stillbirth, or neonatal death. Some studies report no increased risk of perinatal depression [82, 83], while others report increased risk of PPD [84, 85] during subsequent pregnancies. Pregnant women with a history of miscarriage are more likely to have anxiety symptoms [82] and PTSD [85] than those without a history of miscarriage. Some authors report that anxiety tends to be highest in the first trimester [86] and reduces once women pass the point in pregnancy when the previous miscarriages occurred; others report greater anxiety in the second and third trimesters [87]. Anxiety during pregnancy may cause women with a history of miscarriage to limit physical activity more than those without a history of miscarriage [88]. Identification and treatment of anxiety and depression during subsequent pregnancies is critical as psychological distress in pregnancy has been linked with higher rates of miscarriage and other poor obstetric and neonatal outcomes [40].

In summary, depressive and anxiety symptoms are elevated in the first year after miscarriage, especially in the first 4 months, but thereafter, most women have a reduction in symptoms. Women with higher distress levels in the period immediately after pregnancy loss appear to have the highest risk of persistence of symptoms. In women with persisting symptoms, future pregnancies may not be protective. More frequent monitoring for depression and anxiety is warranted up to the birth of the next child for women with perinatal loss. Although there is insufficient evidence to support this, it is prudent to assess women for the psychological effects of prior pregnancy loss before they attempt another pregnancy.

Impact on Fathers and Siblings

Overall, based on the findings of a few small studies, there appears to be a lower rate of distress in men compared to women after a perinatal loss. Men may also grieve differently, preferring to talk less, and present as irritable, and have heavier alcohol consumption [89]. The prevalence of depression for men after a perinatal loss is greatest within the first month post-miscarriage (5–17 %) and then decreases around 6 months post-miscarriage (7 % and 1–4% at 3 and 6 months post-miscarriage, respectively) [90].

Surviving siblings experience the grief of two losses—the loss of their expected sibling and the loss of their parents as they knew them. While supporting parents through a perinatal loss, it is important to gently draw their attention to the possible emotional reactions of their surviving children [91].

Screening

While 30 % of women who miscarried report that they would have liked to discuss causes of miscarriage and risk for future pregnancies, 90 % do not get a follow-up with their provider to allow for this discussion [92]. In fact, women who did not receive a follow-up appointment after their miscarriage to discuss their concerns had higher anxiety symptoms. Six weeks post miscarriage might be the best time for a follow-up as women's responses to miscarriage at 6 weeks predict their responses at 1 year [93].

Commonly used screening instruments include the Perinatal Grief Scale (PGS) [94] which includes three subscales—active grief, difficulty coping, and despair. Although it has a high reliability and convergent validity, it has been criticized for having too much overlap with symptoms of a depressive episode. The Munich Grief Scale [95] is a shorter version of PGS that attempts to more clearly delineate grief from depressive symptoms. The Perinatal Bereavement Grief Scale has been validated in Spanish and English and specifically measures the “yearning” aspect of grief [96]. Another grief scale is the Perinatal Grief Intensity Scale (PGIS) [97]. Generic instruments including GHQ 12 and EPDS can also be used, but are criticized for being sensitive to recent stress, and confounding distress, grief, and depression. There is a dearth of studies examining the utility of routinely screening for psychiatric symptoms or disorders in the aftermath of perinatal loss. Screening this population is challenging as it is difficult to distinguish grief from depression, and normal grief reactions can vary widely in how long they persist. Whether or not one decides to routinely screen for psychological distress, it is important to be aware of risk factors for persisting distress following perinatal loss, and monitor women with risk factors more closely. It is also critical that providers take the initiative to ask pregnant women about their prior pregnancy loss and their current emotional state [81].

Treatment

Some reviews [98] report that psychosocial interventions such as counseling do not improve psychological well-being after miscarriage. Others have found interventions such as the Couples Miscarriage Healing Project, a home-based nurse caring intervention to be effective in the resolution of grief and depression for both men and women [99]. Such couple-based

interventions may be useful to help work through grief and prevent marital discord after miscarriage.

Guidelines for the management of psychological responses after stillbirth are controversial, especially surrounding the parent's decision to hold the baby. Although there is a dearth of randomized controlled trials of bereavement counseling or specialized psychotherapy for mothers, fathers, and families after perinatal death [100], there is evidence from studies using other study designs. Some studies have found that holding the baby may increase the risk of depression, anxiety, and PTSD in the mother, sometimes up to 7 years after stillbirth [101, 102]. However, other studies have found that parents appreciate time and contact with their deceased infant [103], and that parents who see and hold their baby report fewer poor mental health outcomes [104]. Encouragement of parents to see and hold their deceased baby may be best done under guidance from experienced staff [105], always emphasizing the importance of respecting culturally diverse approaches to neonatal death. In the case of termination of pregnancy for fetal anomaly, observing a deformed baby can be traumatic, but it may also help to reduce guilt if observing the baby convinces the mother that she made the right decision [106].

Other approaches to supporting parents grieving after a stillbirth have included supportive DVDs [107], internet-based cognitive behavior therapy [108], and mindfulness-based therapy [109]. Physical activity may help as shown in a recent study, which found that in women within a year of stillbirth, those who reported higher levels of physical activity reported lower levels of depressive symptoms [110].

There is a dearth of studies or reviews specifically examining the use of SSRIs or other psychotropics in the aftermath of perinatal loss. However, it is worth noting that the association between SSRI use and miscarriage is controversial [111], and there is no association between SSRI use and stillbirth [112].

Although all women may not need preventive psychosocial interventions after miscarriage, stillbirth, or neonatal death, it is important that they be monitored, especially if they have established risk factors. Given the lack of evidence for any specific approach, we recommend a customized treatment plan based on the individual's preferences. Elements that are common to all effective interventions include accessibility (home based, internet based, etc.) and making space for the bereaved parents to discuss and experience their loss.

Conclusions

Depressive or anxiety symptoms or disorders are common among women who experience infertility or perinatal loss. Such symptoms can have direct or indirect effects on perpetuating infertility and contribute to poor obstetric outcomes.

Infertility and its treatment are associated with psychological distress. It is crucial to address psychiatric symptoms and disorders among women with infertility because optimal management may improve both maternal mental health and fertility outcomes. Women with risk factors for or symptoms of depression or anxiety should have a comprehensive treatment plan in place that includes evidence-based psychotherapies such as cognitive

behavioral therapy, interpersonal therapy, and couples therapy, and, after a detailed risk benefit discussion, antidepressants if indicated.

Perinatal loss may increase the risk of complicated grief, depression, anxiety, and PTSD, and the risk increases with longer gestation. Women with a history of major depression and lack of social support are at increased risk of developing complicated grief or major depression and thus warrant closer monitoring. We recommend offering a follow-up visit at 6 weeks after perinatal loss and screening for depression and anxiety at that time. Women with a history of pregnancy loss should also be screened during subsequent pregnancies and monitored in the postpartum period after a successful pregnancy. Untreated depression and anxiety are associated with negative pregnancy, birth, and infant outcomes. Therefore, treatment with psychotherapy or medication management when indicated should be offered to optimize maternal and infant health.

Both infertility and perinatal loss are associated with significant psychiatric morbidity, and poor outcomes may be prevented by systematic screening done in conjunction with a system in place to ensure adequate provision of mental health assessment and care. We recommend offering couples counseling, cognitive behavior therapy, or interpersonal therapy to women with known risk factors. Successful pregnancy does not obviate the risk of continuing psychopathology; thus, it is prudent to monitor women with a history of infertility or perinatal loss more closely during subsequent pregnancies. When severity of symptoms warrants it, evidence-based treatments, including antidepressants when indicated, should be offered.

Effective interventions for infertility and perinatal loss are accessible (internet based, home visit based), and focus on acknowledgment of the loss, and making and sharing memories. It is important to encourage enlistment of social support or community groups given the ubiquitous nature of lack of social support as a risk factor for distress following reproductive trauma. Women experiencing infertility or perinatal loss should have a customized management plan that may include education, resources, and the opportunity to discuss their loss.

Conception, pregnancy, and birth are important transitions for women and times when women are vulnerable to psychiatric symptoms and illness. It is critical that women's mental health is addressed at these times in order to optimize maternal and infant health.

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Compliance with Ethical Standards

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Table 1

Infertility treatments [13]

Treatment/evaluation	Description	Common side effects/burden
Females		
1 Ovulation tests—basal body temperature measurement, urine LH, serum progesterone	Measure body temperature everyday immediately on waking up to predict ovulation	Needs to be measured consistently before getting out of bed [14]
2 Pelvic anatomy evaluation—transvaginal ultrasound, hysterosalpingography, MRI, hysteroscopy, laparoscopy		Complications of laparoscopy such as pneumoperitoneum and vascular/bowel injuries
3 Oral medications Selective estrogen receptor modulators (clomiphene) Bromocriptine for hyperprolactinemia	50–150 mg for 5 days a cycle for up to 6 months Oral or intravaginal	Hot flashes, blurred vision, nausea, and headache Dizziness, upset stomach
4 Surgical treatments Laparoscopic ovarian diathermy Fimbrioplasty Tubocornual anastomosis		Increased risk of ectopic pregnancies, pneumoperitoneum and vascular/bowel injuries
5 Assisted reproductive technology	Daily subcutaneous injections for female of GnRH and FSH for 14 days, blood tests	Infection/bruising at injection site, ovarian hyperstimulation syndrome (abdominal pain, nausea, rarely respiratory distress, and pulmonary embolus)
Intrauterine insemination	Placement of washed sperm inside uterus	
In vitro fertilization	Placement of eggs with sperm outside the body followed by transfer of embryos into the uterus	
In vitro fertilization with intracytoplasmic injection	Injection of retrieved eggs with a single sperm followed by transfer of embryos to the uterus	
Males		
1 Semen analysis		
2 Serum FSH, LH, testosterone, and prolactin levels		
3 Epididymal sperm aspiration	Used uncommonly	
4 Testicular biopsy	Used uncommonly	
5 Oral medications Dopamine agonists for hyperprolactinemia Gonadotrophins for pituitary disease		Dizziness, upset stomach
6 Surgical treatments Surgery for obstructive azoospermia Surgical reanastomosis of vasectomy		Risks of invasive surgery

Table 2

Types of perinatal loss

Term	Definition	Epidemiology
Miscarriage/spontaneous abortion	Unintended termination of pregnancy before 20 weeks of gestation.	15–20 % of recognized pregnancies [50]. Risk increases with maternal age [51].
Recurrent pregnancy loss (RPL)	2–3 consecutive pregnancy losses (not required to be intrauterine) [52]. Primary RPL—pregnancy loss in women who have never had a viable pregnancy. Secondary RPL—pregnancy loss in women who have had a previous live birth.	2 to 3 % [53].
Stillbirth	Death of the fetus after 20 weeks gestation/after reaching 14 oz. weight [54]. Fetal death in utero or in the process of delivery.	4.6 per 1000 live births in singleton pregnancies.
Neonatal death: early neonatal death (<7 days), or late neonatal death (7 to 27 days). Includes SIDS	Death of the baby after a live birth and before 28 days after gestation [55].	6.2 per 1000 live births [56]. Neonatal deaths account for nearly two thirds of all infant deaths annually [57].