

Research Article

Women's Experiences and Coping Strategies for Dealing with Recurrent Implantation Failure in IVF/ICSI – An Interview Study

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10 CH 8091 Zürich**Citation:** Meier M, di Giacopo SCM, Stucki P, Birchler K, Leeners B (2024) Women's Experiences and Coping Strategies for Dealing with Recurrent Implantation Failure in IVF/ICSI – An Interview Study. *Gynecol Obstet Open Acc* 8: 226. DOI: <https://doi.org/10.29011/2577-2236.100226>**Received Date:** 7 December 2024; **Accepted Date:** 17 December 2024; **Published Date:** 20 December 2024**Abstract**

Objectives: Despite significant advances in reproductive medicine, embryo transfer (ET) does often not result in the desired pregnancy, which induces a significant psychological burden, results in a reduction in quality of life and the decision to prematurely stop fertility treatment. This qualitative study explores the emotional, psychological, and social impact of recurrent implantation failure (RIF) to provide a basis for better patient support and future research. **Methods:** The semi-structured interview guide included 35 key questions developed on the basis of the available literature and clinical experience of specialists in fertility medicine. A convenience sample of women with at least three consecutive unsuccessful ETs was interviewed. Sample size was determined by achieving satiety, i.e. when no more new aspects were reported. This resulted in a total of 13 interviews, which were analyzed by qualitative content analysis. **Results:** RIF is associated with a broad variety of emotional reactions, of which disappointment, grief, feelings of guilt, struggling with fate, and feelings of helplessness are reported most frequently. The two-week waiting period following ET and the communication of pregnancy results are perceived as particularly stressful. The duration of fertility treatment is associated with increasing strain, especially in the case of augmenting time pressure related to age. Social support and quality of the relationship play a significant role in coping with reactions to a negative pregnancy test after ET. **Conclusions:** To improve patients' emotional well-being and reproductive decisions individualized psychological support using partner relationships and social networks as resources should address the unique emotional trajectory of each woman.

Keywords: Recurrent implantation failure (RIF), emotional experience after embryo transfer, dealing with negative pregnancy tests in IVF/ICSI, female perspective

Introduction

Involuntary childlessness imposes a significant burden on the 8-12% of women affected globally [1,2]. Becoming parents is a central aim of many women and men, and this aim is threatened when a desired pregnancy does not occur. Although reproductive medicine has made significant progress since its inception in 1978 [3], with success rates continuing to rise, most couples have to

undergo several attempts before achieving pregnancy. According to current data from 40 European countries, the mean pregnancy rate in 2019 per embryo transfer (ET) was 34.6% after IVF and 32.1% after ICSI [4]. Although the likelihood of pregnancy increases with the number of treatment cycles [5], nearly 40% of couples do not achieve pregnancy even after the third ET [6]. With at least four ETs, a pregnancy can be achieved in 7 out of 10 couples, leaving approximately 30% of couples who remain childless even after repeated attempts [6]. As a whole, modern reproductive medicine strongly improves chances of pregnancy, but couples still face uncertainty about whether they will become

parents and how many treatment cycles will be needed.

Stress associated with the inability to conceive is well-documented and can negatively impact the emotional and psychological well-being of both men and women [7-10]. Quality of life (QoL), overall well-being and self-efficacy in coping with infertility are known to decrease with each unsuccessful ET [11-13], while levels of anxiety and depression rise [12,14-16]. Approximately 10% of female patients exhibit moderate to severe depressive symptoms after unsuccessful treatment [12]. In addition, unsuccessful fertility treatment frequently has a negative impact on the couple's relationship [10, 17].

An international consensus development study identified the emotional and psychological impact of recurrent implantation failure (RIF) as one of the top 10 research priorities for ART in 2020 [18]. Although the available literature provides a good overview of the psychosocial consequences of persisting undesired childlessness, no study has up to now addressed the full picture of specific reactions to RIF. Available studies focus on depressive and anxious symptoms, while other reactions have been evaluated to a lesser degree or not at all, so that understanding the potential consequences of RIF on the general and mental well-being of would-be parents is shockingly underdeveloped. As a consequence, scientifically sound recommendations and concepts for improving mental health, emotional well-being and related quality of life after RIF are lacking.

To provide a reliable basis for better counselling and future research, this interview study systematically examined the emotional, psychological, and social aspects associated with RIF. By providing a reliable basis from which to adjust support models, we also hope to prevent prematurely abandoned fertility treatment. To collect data for this working basis, we evaluated the (i) type, (ii) dimension, and (iii) development of emotional, psychological, and women's social reactions to at least three consecutive unsuccessful ETs against a background of various confounders. In addition, (iv) related coping mechanisms were analysed.

Methods

The overall study was designed as a mono-centric interview study. Included participants were women either currently undergoing or those who had received in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) within the previous two years and had encountered at least three consecutive unsuccessful ETs. Proficiency in the German language was a further prerequisite for participation. Participants provided written informed consent after comprehensive briefings about the study's objectives. Women with clinically relevant physical or psychiatric diseases potentially influencing study outcomes were excluded.

Recruitment: Potential participants were pre-selected based on their electronic medical charts, contacted by the project management via

telephone or email and informed about the content and objectives of the study in January and February 2023. If interested, they received written study information with the study consent form by e-mail and were invited to an interview. Altogether, 26 women were contacted, of whom 3 (11.5%) could neither be reached by telephone nor responded to our e-mail. Of the remaining 23 women, 13 agreed to participate (response rate 56.5%). Lack of time (13%) and fear of intensifying emotional reactions by being interviewed (4.3%) or further unspecified aspects (26.1%) were reasons given to refrain from study participation.

The sample size was based on information saturation, which is defined as the point when all main categories related to the research question are fully developed and integrated [19]. The interviews were conducted from February to June 2023.

Interview guide: A literature review on emotional and psychosocial reactions to RIF as well as the clinical experience of the investigators both fed into an interview guide for the semi-structured interview that was conducted with each participant. Emotional effects refer to subjective feelings while psychosocial effects encompass a broader interplay between psychological and social factors, shaping behavioural, attitudinal, and adaptive responses to RIF. The aim of the interview was to obtain a comprehensive overview of reactions to RIF by re-evaluating previous findings and adding aspects that had previously received only marginal attention or were possibly completely unknown.

The interview guide contained 35 main questions, each with several optional in-depth questions designed to encourage study participants to share their experiences so as to obtain as complete a picture as possible of all potentially relevant topics in dealing with RIF. Questions were open-ended and narrative-generating with free response options. Question order was flexible to allow for a natural and empathetic interview process that prioritized spontaneous stories rather than an inflexibly structured process. If important topics emerged that had not previously been considered, these were integrated into the updated form of the interview guide.

The qualitative method employed an inductive approach without predefined hypotheses, focusing on describing women's experiences and feelings after RIF.

Data extraction: MAXQDA software [20] was used to transcribe and code the interviews. Participant names were encrypted, and data were stored on a secure server. Content analysis followed Kuckartz and Rädiker's [21] seven-step structured analysis model. Based on the key research questions, initial analysis phases included examination, marking relevant content and creating memos for notes. Subsequent phases involved developing main categories, coding all material, forming inductive subcategories. The systematic analysis aimed to uncover central aspects. The iterative development process ensured the system's internal coherence and alignment with hierarchical abstraction principles.

Ethics: The project was carried out in compliance with the current version of the Declaration of Helsinki and Swiss legislation. Adherence to ethical requirements was confirmed by the local ethics committee. All interviews were conducted only after written informed consent was given by the study participant in question.

Results

		Study participants (N=13)
Age in years	Mean \pm SD ¹ Range	37.7 \pm 3.0 33 – 43
Country of birth		Switzerland Germany Netherlands
Years living in CH	Mean \pm SD Range	13 \pm 7,1 8 – 18
Highest level of education		Apprenticeship University
Duration of partnership in years	Mean \pm SD Range	9,8 \pm 5,1 3 – 23
Cause of infertility		Female factor Male factor Combined female and male factor Unexplained Desire for PID ²
Duration of infertility in years	Mean \pm SD Range	4.6 \pm 2.5 2 – 12
Duration since first evaluation of infertility in years	Mean \pm SD Range	3.7 \pm 2.0 2 – 10
Number of ETs ³	Mean \pm SD Range Mean \pm SD Range	Total number Total number Number unsuccessful ETs Number unsuccessful ETs
Number of women with ≥ 1 child ⁴		Spontaneous conception Through IVF/ICSI
Success of IVF/ICSI at time of interview		Yes No
Time interval between last ET and interview in month	Mean \pm SD Range	8.3 \pm 6.6 2 – 23
<p><i>Note.</i> ¹SD = standard deviation, ²PID = pre-implantation diagnosis, ³ET = embryo transfer. ⁴All children, both prior to the study period were conceived in the current partnership.</p>		

Table 1: Socio-demographic data

Table 1 summarises socio-demographic data for the study group. During the interviews women actively contributed for an average of 46 ± 12 minutes (range 17 – 58 minutes). A total of 8 main categories and 94 subcategories, encompassing 367 different statements, were identified. Psychosocial reactions to RIF were categorized into the topics emotional and psychological well-being, quality of life, self-perception as a woman and relationship. Other main categories were specific reactions in association with different treatment phases, along with development over time and role of the number of ETs, coping strategies and influencing factors. About 7.1 - 2.5 (range 4 – 13) interviews had to be conducted until saturation was reached for all topics. Self-perception as a woman and association with different treatment phases were the categories reaching saturation first (after 4 interviews) and emotional and psychological well-being last (after 13 interviews). Table 2 gives an overview of the experiences that were mentioned by at least 30% of the women.

Topic	Subcategory	N = 13 ¹	
Emotional and psychological well-being	Grief	10 (76.9%)	
	Feelings of guilt	9 (69.2%)	
	Struggling with fate	8 (61.5%)	
	Disappointment	7 (53.8%)	
	Helplessness	6 (46.2%)	
	Emotional rollercoaster	6 (46.2%)	
	Feelings of shock	4 (30.8%)	
	Loneliness	4 (30.8%)	
Quality of life (QoL)	Infertility reported as major factor for reduced QoL	5 (38.5%)	
Self-perception as a woman	No influence on self-perception as a woman	5 (38.5%)	
Relationship	Influence of fertility treatment on the relationship	Positive Negative None	8 (61.5%) 6 (46.2%) 5 (38.5%)
	Sexual problems resulting from infertility which challenge the relationship		5 (38.5%)
	Feelings of guilt towards the partner		4 (30.8%)

Table 2: Reported experiences after RIF in IVF/ICSI

The number of different reactions to RIF varied considerably. Altogether, 7 participants reported 30-35 aspects, 4 women reported 22-25 aspects, and 2 women reported 13-16 aspects. The groups differ notably in the category "Emotional and psychological well-being".

Grief was the most frequently reported reaction to RIF. Expressions of sorrow varied, with some women reporting tears, while others predominantly experienced depressive symptoms. Feelings of guilt were frequently combined with an enduring sense of self-blame and feelings of culpability for not achieving pregnancy or contemplating potential missteps. Irrespective of the indication for fertility treatment (for example female factor, unexplained infertility or PID) women were convinced that they/their bodies were to blame for RIF. The persistent question of why their desire for children remained unfulfilled, together with a comparison with other couples, resulted in a lack of understanding, a sense of fateful disadvantage and the question of whether they might challenge something that was not meant to be. The unsuccessful search for a reason of RIF was a major and stressful issue. One source of frustration was the divergence between the magnitude of the effort invested in achieving the pregnancy and a negative result. During fertility treatment, this led to an emotional rollercoaster including hopeful, disappointed and shocked feelings after a negative pregnancy test. The sentiment of loneliness, sometimes even towards their partner, and especially regarding lack of support in their emotional reactions, permeated the experience, with communication barriers, misunderstanding of the others' needs or differences in coping mechanisms reported as key underlying factors. Guilt emerged as a significant topic, especially in the context of the causal involvement of each partner regarding

infertility. On the positive side, stable supporting relationships, strengthened bonds and increased support from partners, was frequently reported and teamwork during fertility treatment highly appreciated. Tensions occurred more often at the beginning of the treatment but subsided thereafter. Other less frequent emotional reactions included lack of hope, doubt or fear. Some women expressed an exclusive focus on their infertility, occasionally losing sight of life's positives and allowing QoL to deteriorate. RIF was attributed to bad luck and pre-existing diseases, such as endometriosis, but none of the women felt burdened by a self-perception that she was not a fully valid woman.

Association with different treatment phases

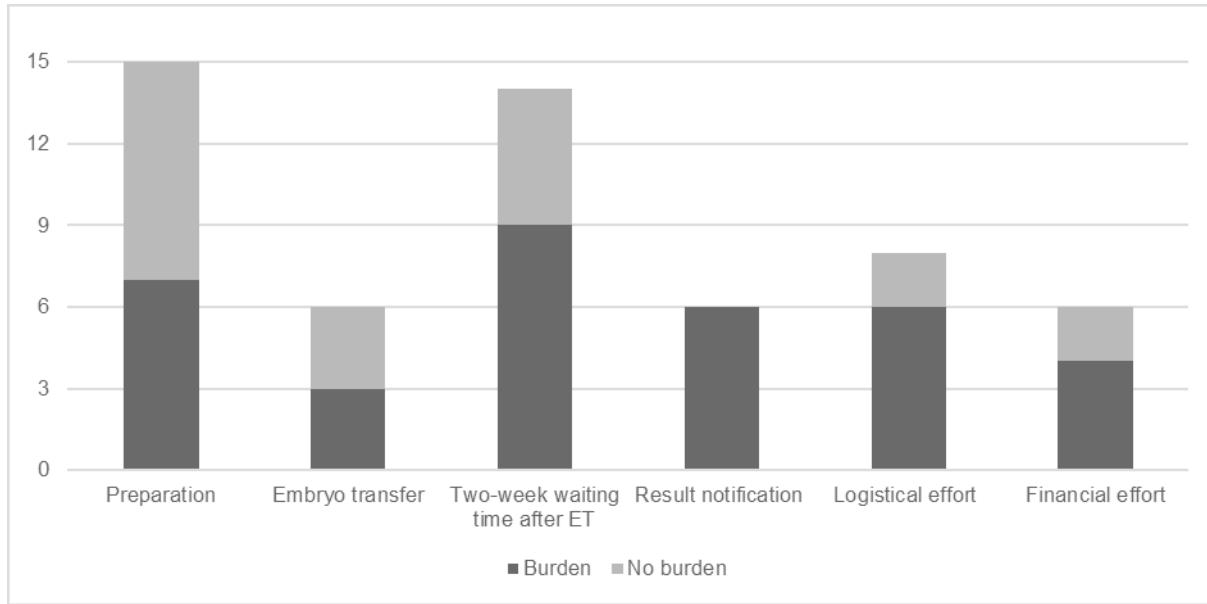


Figure 1: Stressors during different phases of fertility treatment

Note: Some participants experienced both burden and no burden during the same phase, sometimes varying daily or even on an hourly basis. Not all participants explicitly commented on every treatment phase, as this depended on how distinctly they experienced the relevant phase.

A total of 8 women experienced no stress in relation to the physical aspects of treatment, finding hormone injections tolerable, appreciating active involvement, which provided them with a sense of purpose. In contrast, 7 women found the physical aspect challenging due to heightened awareness of hormonal changes, and their bodies altering, as well as increased emotionality during stimulation.

Emotional experience during ET varied between hope and fear, feeling pressure related to embryo quality and implantation, and a lack of specific emotional reactions. A total of 9 women found the waiting period after ET stressful, often describing it as the most difficult time, marked by heightened body awareness and symptom analysis, tension, uncertainty, and lack of an opportunity to actively contribute.

Altogether, 6 women described the results notification process as a burden that caused nervous anticipation before the result was communicated. They also suffered a lack of post-result support. Although, there were clear differences between which period was experienced as most stressful and whether feelings were rather positive or negative during specific phases, result communication was universally perceived as burdensome. Further key stressors were, the challenges of numerous appointments with their related time constraints, inflexibility in treatment, inflexible working hours and the impact of financial burden on treatment continuation as well as insufficient psychological support.

Development over time and the role of the number of ETs

A predominant concern expressed by 92.3% of participants was the perceived increase in stress levels throughout the overall fertility treatment. Almost half of the women (46.2%) cited the prolonged duration of treatment as a significant source of burden. In contrast, 38.5% of participants became accustomed to the treatment failures while simultaneously feeling increased stress.

Factors influencing reactions to RIF

Table 3 provides an overview of factors influencing reactions to RIF. Women emphasized the emotional toll of fertility-related questions from their social environment, leading them to become cautious in asking others about their desire for children and fertility. The weight of social expectations was described as being heightened by media presentations of families and parenthood.

Influencing factor	Study participants N = 13 (%)
Expectation of successful treatment outcome	7 (53.8%)
Positive experience in previous challenging life situations (general life, profession, education)	5 (38.5%)
Negative feeling due to fertility inquiries by social environment (intrusive, lacking in sensitivity)	6 (46.2%)
Positive experience with reacting openly to social pressure	4 (30.8%)
Culture- and family-related social pressure to have a child	4 (30.8%)
Existing child as resource	4 (30.8%)
Emotionally charged evaluation of embryo loss	4 (30.8%)

Table 3: Factors influencing experiences of RIF

Coping strategies

Table 4 provides an overview of coping strategies for RIF. Conversations within the partnership were one of the most frequently applied coping strategies. Women highlighted mutual support, spending quality time together, discussing and sharing non-fertility projects and, especially, laughing together as beneficial. Support was also found in other good relationships, possibly engaging in non-fertility related conversations. At the same time, emotional disclosure outside the partnership proved helpful, with most women seeking social support from a small number of persons of trust (close family members or friends). Reactions from a wider social environment were often mixed, so that feelings of isolation were carefully weighed against burdensome reactions from outsiders. Several women found direct or online exchange with fellow sufferers enriching, or fostering better understanding, creating strong connections, and providing comfort in the knowledge that they were not alone. However, such exchange was also reported to cause additional stress by sharing the burden of others or being exposed to misleading information. Two women kept their experiences entirely within their partnership.

Additionally, fulfilling activities (e.g. contemplating, travelling, sports, focusing on careers), especially when not pregnant was a precondition for these activities, and planning alternative attractive life scenarios as a “Plan B” proved helpful.

Psychological support initiated at different timepoints of the fertility treatment by 31% of the study participants was reported as a key coping element, with the development of new strategies to deal with RIF and a broader context for their experiences being reported as the main success factors.

Strategy	Subcategory	Study participants N = 13
Adaptive coping	Couple-centred coping	9 (69.2%)
	Distraction/focus on other things	10 (76.9%)
	Developing alternative life plans	5 (38.5%)
Social support	Verbal emotional disclosure	6 (46.2%)
	Exchange with persons of trust	8 (61.5%)
	Exchange with fellow sufferer	5 (38.5%)

External support	Psychological support	4 (30.8%)
	Forums/Instagram/Podcasts	7 (53.8%)

Table 4: Women's coping strategies towards RIF

Discussion

To develop a reliable basis for appropriate support models as well as future research, this interview study aimed at providing a comprehensive overview of the emotional, psychological, and social reactions as well as coping strategies associated with RIF. Grief, struggling with one's fate, disappointment, feelings of helplessness and experiencing an emotional rollercoaster proved to be predominant reactions to RIF. Strengthened bonds and increased support from partners during fertility treatment were frequently reported as positive developments. Despite occasional tensions, most relationships remained stable; guilt, however, played a significant role, either in self-blame or attributing blame to partners. The demands of numerous appointments, compounded by logistical challenges and financial stress further contributed strain. Emotional reactions after ET ranged from hope to uncertainty and fear. The post-ET waiting period was characterized by heightened body awareness and high stress levels, while notification of results was even more burdensome. Reactions to RIF were influenced by expectations of treatment success, past life experiences, reactions from participants' social environment, the presence of an existing child and/or one's individual evaluation of failure to become pregnant.

Conversations with and emotional support from partners were key coping mechanisms. Distraction through positive non fertility-related life events, travel, sports, career focus, or considering alternative life plans was beneficial. Seeking emotional support with trusted individuals outside the partnership provided comfort. Interactions with others facing similar challenges and psychological support were further coping resources.

What emotional / psychosocial reactions do women experience after RIF?

As expected and in agreement with previous literature, the emotional and psychological well-being of women facing fertility treatment failure was impaired [12], with grief, guilt and struggling with one's fate being three core themes in our study. Other studies have presented depression and anxiety as common reactions to RIF [14, 12, 16]; however, the experience of depression was mentioned by only one and anxiety by none of our study participants, so that our findings indicate that depression and anxiety are not the only and possibly not the main reactions to RIF. Instead, many other emotional experiences that were subjectively experienced as being more relevant, although currently not systematically addressed in patient support concepts, were reported. The theme of guilt

consistently occurred, comprising self-blame or blame towards the partner. In a previous study, blaming oneself for infertility was associated with increased symptoms of depression and anxiety. However, and understandably, when couples blamed each other, reduced relationship satisfaction was experienced, which is in line with other findings [22].

Fertility treatments are out-of-pocket expenses in Switzerland, and although the participants in this study were predominantly affluent with mostly tertiary education, nearly one-third reported that the cost of treatment was burdensome, which agrees with other results [23]. The burden will likely be even greater in cases of more limited financial resources and may ultimately result in decision against medical assistance to overcome infertility [24]. Interestingly, none of the study participants considered a pre-mature ending of the fertility treatment because of RIF.

As emotional experiences and strategies for dealing with RIF varied starkly among study participants, it would seem that support must be adjusted to the individual relevance of parenthood, reproductive history, fertility treatment and reactions to RIF.

Treatment phases and development over time

Although the post ET waiting time has been recognized as a time of reduced mental well-being, also in comparison to the stimulation phase and oocyte retrieval [11], experiences varied greatly between study participants and included predominantly negative but also positive feelings. Uncertainty and inability to actively contribute to the outcome with resulting feelings of helplessness were the key underlying factors reported, with the latter recognised as a risk factor for developing anxiety and depression [16]. Women with higher levels of education have often experienced success when investing effort towards life aims. Therefore, infertility with its associated lack of control represents a challenge and already developed coping strategies no longer work. What is more these successful women cannot rely on their own resources alone but depend on the support of fertility specialists. The helplessness reported by nearly half of the women reflects this situation very well. The lower psychological well-being in infertile women with lower educational levels [15] underlines that these women may particularly benefit from psychological support.

The duration of fertility treatment impacted the experience of affected women. In our study as well as others, a longer duration of infertility was associated with deteriorating emotional adjustment. This correlation was mediated by the individual importance of

parenthood [25], which was also confirmed by our findings. Women experiencing RIF are known to have reduced quality of life compared to those who have only undergone one treatment [26]; several of our study participants reported growing disappointment in association with each additional implantation failure. Each unsuccessful transfer added additional strain, and with each failed attempt, it became increasingly difficult to maintain hope for success. However, few emotional challenges were direct reactions to RIF; many related to the ongoing situation of unfulfilled desire for children.

Which factors influence the experiences of RIF?

According to our study, the need for and use of social support is highly individual. Social pressure during fertility treatment was a significant issue, one which is also supported by other findings [27]. Study participants reported diverse approaches to handling fertility-related questions from their social environment, for example, using prepared generic responses or distancing themselves if the subject was brought up. On the other hand, social support may serve as a protective factor towards unfavourable emotional reactions [28].

In the present study, social support was sometimes perceived as ambivalent. Some women were reluctant to discuss the topic and therefore only shared it with a limited number of highly selected people. For those who chose open communication, this approach proved to be very helpful. Valuable insights from the experiences of other affected women were particularly emphasised; these also helped to reduce feelings of loneliness. None of the respondents reported negative experiences related to open communication, which may either be explained by selection bias—these women had clearly decided for open communication—or by denial of any negative aspects. Only one woman mentioned the burden of receiving advice.

Which coping mechanisms help women to deal with RIF?

Most coping strategies used by our study participants, for example, couple-centred coping, alternative life plans, talking about RIF, or psychological support, represent emotion-oriented strategies. Other studies have reported problem-oriented coping strategies as the dominant strategy [29]. However, emotion-oriented coping methods have been found to predict better adjustment to unsuccessful fertility treatment [30]. Meaning-based coping strategies, which were also found to be helpful by the participants in this study, are thought to predict lower stress levels than, for example, avoidance [31].

Although most women also reported challenges within the relationship when being confronted to RIF, they valued couple-centred coping, especially conversations with their partner, as the most efficient coping resource, a finding that agrees with other

studies [1]. Half of the study participants described positive effects resulting from the challenges of RIF on their relationship, which is highly relevant as satisfying partnerships facilitate coping with infertility [32], however, women also reported many infertility-related stressful situations. Although relationships may become less stable with an increasing number of unsuccessful treatments [33], the percentage of intact partnerships in our study was very high. This background will likely have influenced the high frequency of couple-centred coping found in our study. As specific interventions, for example, during the two-week waiting period, seem to reduce burden [34], the findings on the most appreciated coping strategies in our study may be used to further improve the efficacy of such interventions.

Strengths/Limitations

To our knowledge this study is the first to provide a comprehensive overview of potential reactions to and coping strategies for RIF. The completion of spontaneous narratives with preselected questions allowed participants to individually define reactions and express the importance of different aspects of coping, while receiving feedback on aspects developed from the literature and our clinical experience at the same time. The sample size is within the typical range of qualitative exploratory interview studies [35, 36] but obviously it is far from the number needed for even descriptive quantitative statistics. The sample was heterogeneous in terms of backgrounds and reproductive histories, which helped to obtain a comprehensive picture of the experience of RIF. Also, the timeframe between the last ET and the time of the interview varied and some of the fertility treatments had finally been successful before the interview, which might have introduced recall bias. As a further limitation, most of the women had a high level of education, thus limiting the generalisability of the results. The content analysis coding process was limited to a single coder, which prevents the consideration of inter-coder reliability, a criterion of qualitative content analysis validity.

Implications for further research

Future research should be based on larger study groups to allow analysis in specific subgroups. Also, data collection should be conducted prospectively at predefined time points of fertility treatment to better understand specific reactions to different aspects of the treatment and longitudinal development. Type and effects of ideal coping interventions on the background of individual patients' characteristics should be further evaluated. In particular, the reduction of feelings of guilt should be explored for its potential to increase quality of life in the context of RIF.

Conclusion

The analysis of the effects of RIF on women underscores the profound and multifaceted emotional impact of this experience.

The prevalence of emotions such as sadness, helplessness and guilt highlight the deep psychological burden that RIF imposes, often exacerbated by the length of treatment rather than by the mere number of unsuccessful attempts. Importantly, the partnership and social support networks emerge as vital buffers against the loneliness and distress associated with RIF. These findings emphasize the need for individualized psychological support that addresses the unique emotional trajectories of each woman.

Authors' roles

M.M and B.L designed the study; M.M conducted the interviews and analysed data. M.M and B.L. defined the concept for the analysis and drafted a first version of the final manuscript. S.C.M.d.G, P.S and K.B. revised the manuscript critically. S.C.M.d.G focused on a search of previous literature. All authors approved the final version of the manuscript.

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Research data statement

Data are available from the corresponding author upon reasonable request.

Competing interests:

None of the authors has any conflict of interest.

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