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Title

Adjustment to unmet parenthood goals: Systematic review of long-term adjustment after failed fertility treatment

Running title

Adjustment to unmet parenthood goals

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Abstract

43
44 **Background:** Fertility treatment is not guaranteed to succeed and around 30% of patients do
45 not achieve parenthood. Failed treatment represents the loss of parenthood and often
46 triggers intense and prolonged grief reactions. There is an increasing awareness of the need
47 to support patients in the aftermath of failed treatment, however there are no effective
48 interventions for the effect. This need for support is expected to increase as the number of
49 people delaying parenthood increases and therefore so does the number for whom assisted
50 reproduction will not offer a solution.

51 **Objective and rationale:** This mixed-methods review aims at investigating if patients who
52 undergo failed fertility treatment experience significant psychosocial adjustment difficulties
53 that warrant the provision of psychosocial support, and at developing a comprehensive
54 model of adjustment to unmet parenthood goals that can be used to assist the design of
55 theory led psychosocial interventions.

56 **Search methods:** Five databases were systematic searched between 1978 and December
57 2015. Search terms included fertility treatment AND psychosocial adjustment AND post-
58 treatment. Quantitative studies had to include group mean comparisons on psychosocial
59 adjustment (mental-health, wellbeing) between patients who did failed treatment and a
60 control group. Qualitative studies had to focus on experiences of psychosocial adjustment
61 after failed treatment. Screening, data extraction and critical appraisal were done
62 independently by the authors using pre-defined protocols. Two meta-analyses were
63 performed on mental-health and wellbeing with a random effect model. Primary outcome was
64 Hedge's g. Publication bias was checked with visual inspection of funnel plots, Egger's test
65 and the trim-and-fill method. A 3-stage thematic analysis of results reported in primary
66 qualitative papers was implemented. First-order descriptive and second-order interpretative
67 themes were extracted.

68 **Outcomes:** Nine quantitative (9052 individuals, 8 countries) and 9 qualitative (267
69 individuals, 6 countries) studies were included. Six (67%) of the quantitative studies reported
70 on mental-health and 7 (78%) on wellbeing. The meta-analyses showed that the failed group
71 had worse mental-health ($g = -0.450$, $P=0.002$, 95%CI [-0.734 -0.267]; $I^2=85\%$, $P<0.001$) and
72 wellbeing ($g = -0.319$, $P<0.001$, 95%CI [-0.439 -0.198], $I^2=45\%$, $P=0.001$) than controls. The
73 qualitative review resulted in 28 first-order themes that were grouped into 6 second-order
74 themes: individual and relational adjustment, social adjustment, acceptance, pursuit of new
75 life goals, meaning making, and fertility care perceptions and needs. The data showed that
76 individual, relational and social adjustment tended to increase with time since treatment, and
77 that individuals' care perceptions and needs also changed. The data also suggested that
78 individuals who engage in the psychological tasks of accepting and making meaning of their
79 situation and pursuing new life goals adjust better and have fewer support needs. These

80 predictions were articulated in the Three Tasks Model of Adjustment to Unmet Parenthood
81 Goals.

82 **Wider implications:** Results provide compelling evidence for the provision of psychosocial
83 care directed at helping individuals relinquishing their parenthood goals. The model
84 developed offers comprehensive guidance on the therapeutic mechanisms that psychosocial
85 care should target to promote adjustment. Future research should test the model with
86 prospective cohorts studies or by developing and testing interventions based on its
87 predictions.

88
89 **Key-words:** parenthood; infertility; childlessness; psychosocial adjustment; mental-health;
90 wellbeing; psychological care; mixed-methods; systematic review; meta-analysis.

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Introduction

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96 Around 10% of individuals experience infertility and half of these undergo fertility
97 treatments such as intra-uterine insemination (IUI) or In-Vitro Fertilization (IVF) to conceive
98 (Boivin et al. 2007), (Datta et al. 2016). For most people fertility treatment represents their
99 only chance to achieve their parenthood goals, that is, to have the number of children they
100 desire. However, treatment is not guaranteed to succeed and around 30% of patients do not
101 achieve parenthood or end up having less children than they would like to (Pinborg et al.
102 2009, Troude et al. 2016). For these people the remaining options are to forgo their
103 parenthood goals or apply for adoption. Therefore, for thousands of people failed fertility
104 treatment represents the loss of biological parenthood, or parenthood in general, and usually
105 triggers intense and prolonged grief reactions (Daniluk 2001, Volgsten et al. 2010). There is
106 an increasing awareness of the need to support individuals in the aftermath of failed fertility
107 treatment and of the preventive role fertility clinics can play in this context (Gameiro et al.
108 2013). However, the recently published guidelines of the European Society for Human
109 Reproduction and Embryology (ESHRE) could not list a single evidence-based intervention
110 with this aim, suggesting that patients' support needs are not being addressed (Gameiro et
111 al. 2015). This support need is expected to increase as the number of people delaying
112 parenthood increases and therefore so does the number for whom assisted reproduction will
113 not offer a solution (Leridon 2004). The present mixed-methods review aims to investigate if
114 patients who undergo failed fertility treatment experience significant psychosocial adjustment
115 difficulties that warrant the provision of psychosocial care and at developing a
116 comprehensive model of adjustment to unmet parenthood goals that can be used to guide
117 the design of psychosocial interventions.

118 Despite the call for psychosocial care in the aftermath of treatment (Gameiro et al. 2015),
119 it is still unclear if individuals who do failed treatment adjust significantly worse than those for
120 whom treatment is successful. Identity theories (Thoits 1992) would suggest this to be the
121 case because failed treatment represents the loss of parenthood. For some it may only
122 represent the loss of biological parenthood, for others the complete loss of parenthood, and
123 for others yet the impossibility to have more children. Despite the significant differences in
124 these experiences, in this article and we will only refer generically to the loss of parenthood
125 or parenthood goals.

126 Research has shown that undesired childlessness is associated with poorer psychosocial
127 adjustment (e.g., Graham 2015) and those using fertility treatment can be considered
128 especially at risk for maladjustment because of their high commitment to become parents.
129 Indeed, 84% of patients undergo all treatment cycles recommended by their physician
130 (Gameiro et al. 2013) despite treatment being emotionally and physically demanding and
131 disruptive of personal and professional routines. During the last decade several studies

132 investigated adjustment after failed treatment but so far the evidence is mixed. Some studies
133 show impairments in mental-health and wellbeing for patients who experienced failed
134 treatment (e.g., Kuivasaari-Pirinen et al. 2014, Yli-Kuha et al. 2010) but others do not
135 (Hammarberg et al. 2001, Wischmann et al. 2012). This inconsistency may be partially
136 explained by the conceptual and methodological heterogeneity observed.

137 First, different comparison groups were used. Researchers either compared patients who
138 ended successful versus failed treatment (treatment outcome), or patients with children
139 versus without children at the end of treatment (parenthood status). While the first approach
140 is based on the assumption that it is the non-realization of the individuals' parenthood goals
141 that hinders adjustment (less children than desired), the second is based on the assumption
142 that it is their parenthood status (no children at all). These two factors (unmet parenthood
143 goals, parenthood status) are difficult to disentangle and there is evidence to suggest that
144 they interact, whereby the inability to have a(nother) desired child results in higher suffering
145 for childless than non-childless individuals (Gameiro et al. 2016). Second, sometimes the
146 failed treatment group included individuals who already had children before treatment or who
147 adopted or conceived spontaneously after treatment and this may have attenuated group
148 differences in adjustment. Third, the follow-up assessment period varied from immediately
149 after treatment to up to 20 years after, which may have created mixed results because loss
150 reactions are expected to attenuate with time (Bonanno 2004). A meta-analysis taking these
151 potential moderators into account can clarify on the severity of adjustment difficulties
152 experienced after failed fertility treatment.

153 Another important issue is to understand how to support people in the aftermath of failed
154 fertility treatment. So far researchers focused on understanding short-term reactions to failed
155 treatment cycles (e.g., Berghuis and Stanton 2002, Terry and Hynes 1998). The study of
156 long-term (i.e., more than 1 year after) adjustment to unmet parenthood goals is still an
157 emergent research topic within the field that has mostly been investigated with qualitative
158 research methods aiming to describe patients' experiences and needs during the post-
159 treatment period. To date only a few studies focused on identifying risk factors or exploring
160 the mechanisms of adjustment after failed treatment (e.g., Verhaak et al. 2007), despite the
161 existence of multiple psychological theories that can be used for the effect. In the following
162 paragraphs we briefly describe the theoretical paradigms that have been used so far and
163 related evidence.

164 Stress and coping theory states that adjustment depends on the fit between the stressor
165 experienced and the strategies used to address it (Lazarus and Folkman 1984). Stanton and
166 colleagues (1994) hypothesize that when stress results from a significant loss the use of
167 emotional approach coping strategies, such as efforts to acknowledge, understand and
168 express emotions, should promote adjustment, while emotional avoidance strategies have

169 been found to hinder it (Berghuis and Stanton 2002). The only two studies that investigated
170 coping after failed treatment showed that (active and passive) avoidant emotional coping was
171 associated with higher distress up until 5 years after treatment (Daniluk and Tench 2007,
172 Peterson et al. 2009). In addition, meaning based coping was associated with lower personal
173 and relational distress for women, but higher social distress for men (Peterson et al. 2009).
174 Other risk factors for long-term maladjustment were lack of alternative non-parenting roles
175 and social support. The latter may hinder the use of emotional approach coping. Cross
176 sectional studies that investigated adjustment to definitive childlessness had similar findings
177 (Kraaij et al. 2009, Lechner et al. 2007). In addition, these studies showed that cognitive
178 coping is also important for adjustment. While catastrophizing (i.e., emphasizing the negative
179 aspects of childlessness) was associated with worse adjustment, positive reappraisal coping
180 (i.e., attaching a positive meaning to childlessness in terms of personal growth) was
181 associated with better adjustment.

182 Self-regulation theories hypothesize that when all treatment options are exhausted and
183 parenthood goals are highly blocked, individuals who disengage from parenthood and
184 engage in other meaningful goals adjust better than individuals who remain engaged
185 (Heckhausen et al. 2001). Findings from studies focusing on undesired childlessness
186 support this view from both a behavioural and cognitive perspective (e.g., Heckhausen et al.
187 2001, Kraaij et al. 2009). However, research shows that people take time to disengage from
188 parenthood: 44% of individuals still desire to have (more) children 3 to 5 years after ending
189 treatment (Verhaak et al. 2007), 25% 10 years after (Wischmann et al. 2012), and 6% 11 to
190 17 years after (Gameiro et al. 2016). As hypothesized by identity theories (Thoits 1992),
191 childlessness seems to be especially distressing when parenthood is an essential goal in life
192 or when people have few alternative identities or goals (McQuillan et al. 2003, Moura-Ramos
193 et al. 2012).

194 According to the dual process model of grief (Stroebe and Schut 1999), adjustment to loss
195 depends on peoples' ability to process the loss and, in addition, its implications, for instance
196 the impact it may have on the partnership. Around 42% of individuals experience symptoms
197 of complicated grief after ending fertility treatment (Lechner et al. 2007). For some individuals
198 these symptoms can extend until menopause and be re-experienced when other parenthood
199 milestones (e.g., grandparenthood) are not achieved (Daniluk 2001, Wirtberg et al. 2007).
200 Cognitive Behavioural models of grief (Boelen et al. 2006) explain the recurrence of grief
201 symptoms by the difficulty individuals have to integrate the loss into their autobiographical
202 knowledge. These models also claim that grief reactions are augmented by negative beliefs
203 about the loss, for instance the idea that not having a(nother) child will threaten the
204 partnership. Finally, as was observed in the Daniluk et al. (2007) study, avoidance seems to

205 be associated with grief symptoms (Boelen et al. 2006), and it is known that individuals
206 experiencing undesired childlessness tend to avoid the 'fertile world' (Volgsten et al. 2010).

207 Overall these theories highlight the benefits of integrating the loss of parenthood goals
208 and focusing on other goals, and the central role that cognition has in this process. Other
209 theories of adjustment to stressful life events also highlight that individuals strive to find
210 meaning in crises and to regain self-worth and a sense of control over their lives (e.g., Taylor
211 1983). However, none of these theories fully captures the specificities of the parenthood goal
212 that influence how individuals adjust to its loss. For instance, the loss is never definitive until
213 women achieve menopause, it is invisible, in the sense that there are no exterior signs of the
214 loss (e.g., no body), it centres around a goal that was not yet achieved and it is often a loss
215 that is shared with one (partner) or more (family) people. We argue that added value will be
216 gained from developing a model that describes the specific psychological mechanisms that
217 underlie adjustment to unmet parenthood goals and identifies unique risk factors for
218 maladjustment in this context. Such model can set the basis for increasing awareness about
219 the negative psychological impact of not realizing one's parenthood goals and to guide the
220 provision of psychosocial care in this context.

221 In sum, it is still unclear if individuals who experience failed fertility treatment need
222 psychosocial care and what such support should entail. The goals of the present mixed-
223 methods review were threefold. First, a meta-analysis was performed to investigate if
224 individuals who experience failed fertility treatment present worse mental-health and
225 wellbeing than individuals for whom treatment is successful. We distinguished between
226 mental-health, which captures the absence of psychopathological symptoms, and wellbeing,
227 considered to be a more holistic and subjective evaluation of one's life satisfaction or
228 happiness (Diener 2000). Second, moderation analysis were performed to investigate if
229 group differences in adjustment vary with the type of comparisons performed, the percentage
230 of children in the unsuccessful group, the follow-up period considered and the quality of the
231 studies. Third, a review of the existing qualitative research was conducted based on thematic
232 analysis (Thomas and Harden 2008) to extract information about the patients' perceived
233 experiences of this period. Based on the qualitative data, we made inferences about the
234 underlying mechanisms of adjustment to unmet parenthood goals and the risk factors for
235 maladjustment, which we present in the form of a comprehensive model.

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Methods

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Systematic search

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The electronic databases of Medline, Embase, PubMed, PsychInfo and Web of Science were searched between 1978 (the year of the first IVF treatment performed) and December

242 2015 (inclusively) based on search terms for fertility treatment, defined using terminology
243 from the International Committee for Monitoring Assisted Reproductive Technology and the
244 WHO-revised glossary of Assisted Reproductive Technologies (e.g., artificial insemination,
245 assisted reproduction, in vitro fertilization, IVF; Zegers-Hochschild et al. 2009), AND
246 psychosocial adjustment (e.g., adjustment, adaptation, wellbeing, mental-health, quality of
247 life) AND post-treatment (e.g., post, following, after). The detailed search strategy is
248 presented in Table S1 of the supplementary material. The search was adapted for each
249 database. Medical Subject Headings (MeSH) terms were used in PubMed. No restriction was
250 made on the type (journal, conference paper or dissertation) or language of publication. All
251 citations were transferred to EndNote (Thomson Reuters, San Francisco, CA, USA). The
252 results were crosschecked with five articles that had been identified previously as being
253 eligible for the review to ensure the search was suitable for its purpose. The reference
254 sections of all identified articles were examined to identify other relevant manuscripts.

255

256 ***Inclusion and exclusion criteria***

257 This systematic review included quantitative and qualitative studies. Studies were
258 included if they reported on the psychosocial adjustment of a group of individuals (women,
259 men or couples) who experienced failed fertility treatment and if assessments were
260 conducted at least one year after the last treatment cycle. This is the period recommended to
261 ensure patients have definitely finished treatment (Gameiro et al. 2013). Further, literature on
262 stressful life events shows that people take on average 2 years to adjust (Bonanno 2004).
263 Therefore, a minimum period of 1 year allowed us to focus on long-term reactions to loss and
264 not on the immediate short-term distress. To be included quantitative studies had to report on
265 the mental-health or wellbeing of individuals who experienced failed fertility treatment (i.e.,
266 failed group) and a control group. Qualitative studies had to report on a group of individuals'
267 stated experiences of psychosocial adjustment after failed fertility treatment.

268 AF screened the titles and abstracts and AF and SG independently screened the full
269 articles. Any disagreements were resolved with discussion. Duplicate or secondary
270 publications on the same sample reporting on the same outcome were excluded from the
271 meta-analysis to avoid multiple publication bias. In these cases the paper with the most
272 appropriate research questions for the review was prioritized. If this criterion did not apply,
273 the publication reporting data for the largest sample was selected. Excluded studies were
274 classified according to reason for exclusion (see Figure 1).

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280 Data extraction*281 Quantitative studies*

282 AF extracted data using a standardised protocol. To characterise the set of studies, we
283 extracted data (where available) regarding the authors and country, type of fertility treatment
284 (e.g. IUI, IVF), type and size of failed and control groups, whether the failed treatment group
285 included individuals with children (adoption or spontaneous conception), years since the last
286 treatment cycle, study design (cross-sectional or longitudinal) and outcomes reported
287 (mental-health, wellbeing). AF also extracted the necessary quantitative data to include in the
288 meta-analytical syntheses of group comparisons. SG reviewed data extraction and
289 disagreement was resolved via discussion until consensus was reached.

290 Qualitative studies

291 SG extracted data using a standardised protocol. To characterise the set of studies, data
292 was extracted (where available) regarding the authors, country and goal of the study, study
293 sample and percentage with children, study design, years since treatment, and data
294 collection and analytical method. The data extracted for analysis was the content of the
295 results section of each study.

296

297 Data synthesis and analysis*298 Quantitative studies*

299 To investigate group mean differences in mental-health and wellbeing between patients
300 who experienced failed fertility treatment and an adequate control group two meta-analyses
301 were carried out. Only one effect size was returned per study to create an independent set of
302 effect sizes for each analysis. For mental-health we considered measures of anxiety,
303 depression, mental-health, psychopathology or stress because all report on the participants'
304 level of psychopathologic symptoms. We did not include studies reporting on the frequency
305 of specific mental-health diagnosis (e.g., mood disorder) because frequency data cannot be
306 pooled together with group means. For wellbeing we considered measures of general
307 wellbeing, life satisfaction, quality-of-life, general health or vitality, because they capture
308 participants' subjective evaluation of their positive functioning. For studies that reported on
309 multiple measures for the same outcome, specific measures were prioritized. For mental-
310 health, depression was prioritized because it is the measure that best captures the emotional
311 response to the outcome of treatment (Verhaak et al. 2007), followed by mental-health,
312 anxiety, distress and psychopathology. For wellbeing, satisfaction with life was prioritized
313 because it is one of the most commonly used measures in the parenthood literature, followed
314 by quality of life, wellbeing, general health and vitality. If the study reported data for couples,
315 extraction of data took in consideration if the non-independence between male and female

316 data was addressed (Kenny et al. 2006). If it was not taken in consideration either the male
317 or female data were used to ensure independence, women were prioritized because they are
318 more negatively impacted by failed treatment (e.g., Verhaak et al. 2005).

319 A random effects model was adopted due to the heterogeneity of our studies (Borenstein
320 et al. 2009). The I^2 index was used to assess the proportion of effect size variability that was
321 due to non-chance factors (Higgins et al. 2003). I^2 values of 0%, 25%, 50% and 75% indicate
322 no, low, moderate and high heterogeneity, respectively. The probability level of $P < 0.05$ was
323 used to indicate statistical significance. The primary outcome measure used in the meta-
324 analyses was the standardized mean difference between the unsuccessful and control
325 groups. Hedge's g correction was used to adjust for potential bias due to the small sample
326 sizes found in our studies (Borenstein et al. 2009). Effect sizes were aligned across studies
327 so that a negative standardized mean difference indicated poorer adjustment for the failed
328 treatment group than the control group. Effect sizes of .20, .50 and .80 should be interpreted
329 as small, medium and large, respectively (Cohen 1992).

330 To investigate the moderation effect of type of control group (based on treatment
331 outcome, parenthood status), existence of children in the failed treatment group (no, yes)
332 and years since last treatment cycle subgroup (X^2 test) and meta-regression (Z-test,
333 unrestricted maximum likelihood) analyses were done. We used Comprehensive Meta-
334 Analysis version 2.2.064 (Biostat, Englewood, USA).

335 *Qualitative studies*

336 Methods of qualitative reviews are emergent and still subject of debate. In this review we
337 opted to follow the synthesis method described by Thomas and Harden (2008). It was
338 designed to identify which interventions need to be developed to address a particular health
339 issue by understanding it from the point of view of the people targeted. We conducted a 3-
340 stage thematic analysis (Dixon-Woods et al. 2005). The first two stages were descriptive.
341 First, SG extracted all results sections verbatim and SG and AM conducted an independent
342 'line by line' coding of the text to develop descriptors of post-treatment experiences. Two
343 meetings were conducted to contrast and review the descriptors generated. Disagreement
344 was resolved by discussion until the coders agreed if a descriptor should be changed, added
345 or removed from the final list. Second, after a definitive list of descriptors was agreed on, SG
346 developed first order descriptive themes to group the descriptors. The themes needed to
347 capture something important about the data in relation to the research question, representing
348 some level of patterned response across the studies' data (Braun and Clarke 2008). We only
349 considered themes that appeared more than twice across all results and were present in at
350 least two different papers. AF reviewed this process and disagreements were solved by
351 discussion until both authors agreed on the grouping of descriptors and the labels of the
352 second order themes. The last stage was interpretative. SG generated second order

353 analytical themes that were sufficiently abstract to include or explain all first order themes.
354 This process aimed to create interpretative constructs and testable hypothesis (Thomas and
355 Harden 2008) and constituted the crucial step to develop an explanatory model of adjustment
356 after failed treatment. Finally, SG wrote a narrative summary and developed a graphical
357 depiction of the data. AF reviewed SG's analysis and a similar discussion meeting was
358 conducted to reach agreement on the themes and on their graphical and textual depiction.
359 The percentages of agreement in the coding of the first and second order themes were
360 calculated.

361

362 ***Risk of bias assessment***

363 *Quantitative studies*

364 AF and SG designed a critical appraisal form to assess study quality in terms of
365 population representativeness of the study sample (3 points), measurement validity (1 point)
366 and reliability (1 point), and evaluation of research hypotheses (3 points). These criteria are
367 described in detail in Table S3 of the supplemental material. Each study quality score could
368 range from 0 to 8. Papers were classified into low [≤ 2], moderate [3-5] or high [≥ 6] quality
369 studies. AF and SG independently assessed study quality using the form and disagreement
370 was resolved via discussion until consensus was achieved. Subgroup analyses were
371 performed to investigate if the pooled estimates varied as a function of study-quality.
372 Publication bias was checked with visual inspection of funnel plots (Hedge's g against its
373 standard error) and Egger's test (Egger et al. 1997). Trim and fill was used to adjust the
374 standardized mean difference between the failed and control groups for the presence of
375 publication bias (Duval and Tweedie 2000).

376 *Qualitative studies*

377 Two possible sources of bias were considered: the quality of the primary research and the
378 researchers. The quality of primary research was assessed using the Critical Appraisal Skills
379 Programme Qualitative Research Checklist (10 criteria, Critical Appraisal Skills Programme
380 (CASP) 2013), http://media.wix.com/ugd/dded87_29c5b002d99342f788c6ac670e49f274.pdf
381 (see Table S7 of supplementary material). Based on the number of met criteria, each study
382 was classified as being of low [≤ 3], moderate [4-7] or high [≥ 8] quality.

383 As in any qualitative analysis, the researchers' previous understandings may have shaped
384 their interpretation of the data. SG has been researching the psychosocial issues of infertility
385 for around 10 years and has in-depth knowledge of the field literature, including of the post-
386 treatment period. AF is a medical student with no knowledge on this topic prior to the start of
387 the study. None of the authors has regular contact with individuals from the study population.
388 In order to increase the trustworthiness of the findings and reduce possibility of researcher
389 bias, AF and SG independently assessed study quality and disagreement was resolved via

390 discussion until consensus was reached. The themes had to be closely linked to the data
391 collected (Braun and Clarke 2008). As a final step, the findings were presented to a group of
392 five infertility researchers and to a group of six patients and revised according to the
393 feedback received.

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Results

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Description of studies

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Figure 1 around here

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Table 1 around here

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Figure 1 presents the study decision-flow chart whereby 18 studies were included in the mixed-methods systematic review. The systematic search returned 6397 non-duplicated records. Ninety-eight per cent of these studies (n = 6265) were excluded based on their title and abstract, which reduced the number of eligible studies to 132. From these 15 were retained after inspection of the full text and three further studies were identified through the inspection of references lists. The three most common reasons for exclusion were that assessment was done during the first 12 months after treatment, the paper did not report on primary research or the paper did not focus (nor reported) on psychosocial adjustment (see Table S2 of supplementary material for reasons for exclusion). During this process we contacted seven authors to clarify about missing or inconsistent data. Only two replied with the required information.

Table 1 presents the characteristics of the nine included quantitative studies (designated in the reference list by asterisks). The studies sampled 2278 individuals with failed fertility treatment from seven countries. All participants had undergone IVF but some also underwent other treatments including ICSI and gamete intrafallopian transfer (GIFT). Two types of control group were used, based on the outcome of treatment (successful, 33%) or on parenthood status (with children, either adopted or conceived spontaneously or with treatment, 67%) at time of assessment. The time since last treatment varied from one (12 months) to 20 years. Two studies (22%) had a longitudinal design. Only three studies (33%) had a response rate of 80% or higher. Six (67%) studies reported on mental-health and six on wellbeing.

Quality ratings for the studies are also shown in Table 1. Study quality ratings indicated no low, seven moderate (78%) and two high-quality studies (22%) (See Tables S3 to S6 in

426 supplementary material for details on quality assessment). The percentage of agreement
427 between SG and AF on quality ratings was 93%.

428 *Table 2 around here*

429

430 Table 2 presents the characteristics of the nine included qualitative studies (designated in
431 the reference list by asterisks). The studies sampled 267 individuals who experienced failed
432 treatment from six countries. In six studies (67%) the sample included people with children.
433 Eight studies (88%) were cross-sectional and one (12%) was longitudinal with three follow-up
434 assessments occurring more than one year after treatment (Daniluk 2001). Data was
435 collected via interviews and the most common analytical technique was phenomenological
436 analysis (n = 4, 44%), but thematic, content and discourse analysis and grounded theory
437 were also used.

438 Quality ratings for the qualitative studies are also shown in Table 2. Study quality ratings
439 indicated no low, two moderate (22%) and seven high-quality studies (78%) (See Table S7 in
440 supplementary material for details on quality assessment). The percentage of agreement
441 between SG and AF on quality ratings was 83%.

442

443 ***Quantitative meta-synthesis: Psychosocial adjustment after failed fertility treatment***

444

445 *Figure 2 around here*

446

447 *Mental-health*

448 Six studies reported data on group mean differences for at least one mental-health
449 measure that could be included in the meta-analysis. Depression scores were considered for
450 four studies, mental-health for one (Gameiro et al. 2016) and anxiety for one (Leiblum et al.
451 1998). One study reported on frequency of diagnosis (Yli-Kuha et al. 2010) and could not be
452 included.

453 Figure 2 shows the pooled standardized mean differences in mental-health and wellbeing
454 between the failed and control groups for the random effects model. The meta-analysis
455 showed that the failed treatment group had significantly worse mental-health than the control
456 group (g = -0.496, P=0.001, 95%CI [-0.791 -0.200]), with significant heterogeneity between
457 studies (I²=86%, P<0.001).

458 The Egger's test indicated the presence of publication bias (intercept= -3.192, t = 4.85, P
459 = 0.004), which was confirmed through visual inspection of the funnel plot. The trim and fill
460 method also confirmed the presence of publication bias. This method identified one missing
461 study, estimating an adjusted point estimate of -0.458 that was still significant (95% CI -0.726
462 -0.189).

463

464 *Table 3 around here*

465 Table 3 presents the standardized mean differences for mental-health and wellbeing
 466 between the failed and control groups for the pre-defined moderators. Subgroup analysis for
 467 the type of group comparisons done showed that mean group differences were bigger when
 468 the control group is based on the outcome of treatment than when it is based on parenthood
 469 status. The remaining subgroup and meta-regression analyses were statistically non-
 470 significant.

471

472 *Wellbeing*

473 Six studies reported data on group mean differences for at least one wellbeing measure
 474 that could be included in the meta-analysis. Life satisfaction scores were considered for three
 475 studies, quality of life for two (Weaver et al. 1997, Wischmann et al. 2012) and wellbeing
 476 (Johansson et al. 2010) for one. The meta-analysis showed that the failed treatment group
 477 had significantly worse wellbeing than the control group ($g = -0.415$, $P < 0.001$, 95%CI [-0.627
 478 -0.203]), with non-significant heterogeneity between studies ($I^2 = 53\%$, $P = 0.059$). Visual
 479 inspection of the forest plot (see Figure 1) suggests that the study by Leiblum and colleagues
 480 (1998) can be considered an outlier (its effect size was more than twice the pooled standard
 481 deviation distant from the pooled effect size). Therefore we repeated the meta-analysis
 482 excluding this study. The meta-analysis still showed that the failed treatment group had
 483 significantly worse wellbeing than the control ($g = -0.324$, $P < 0.001$, 95%CI [-0.454 -0.193]),
 484 with no heterogeneity between studies ($I^2 = 0\%$, $P = 0.552$). Subsequent analyses were run
 485 without including this study.

486 The Egger's test indicated no presence of publication bias for wellbeing (intercept = -
 487 0.523, $t = 0.428$, $P = 0.349$). The trim and fill, however, identified one missing study,
 488 estimating an adjusted point estimate of -0.298 that was still significant (95% CI -0.422 -
 489 0.175).

490 Subgroup and meta-regression analyses could only be performed for the moderators
 491 existence of children in the failed treatment group and years since treatment and none were
 492 statistically significant.

493

494 ***Qualitative meta-synthesis: Patients' perceived experiences of the period after***
 495 ***failed treatment***

496 To illustrate the analysis process, please consider the following lines of text presented in
 497 the study by Boden (2007): "On a positive note, many couples expressed their belief that the
 498 experience of treatment had enhanced their relationship with their partner, bringing them, as
 499 participants described, 'closer together'".

500 To summarize these data the following descriptor was developed: 'treatment strengthens
501 the relationship'. After, this and other similar descriptors, for instance 'stronger partnership as
502 result of infertility and treatment experience' and 'treatment strengthens the marital
503 relationship and leads to marital satisfaction', were grouped into the first order theme
504 'treatment strengthens partnership'. Finally, this and other first order themes, for instance,
505 'intense grief', 'anger directed at everything and everyone', 'sexual difficulties' and 'men stoic
506 and supportive of their partner' were classified into the second order theme 'Individual and
507 relational adjustment'. Table S8 of the supplemental material presents, for each study
508 included, the list of descriptors of post-treatment experiences and their classification into first
509 and second order themes. Inter-coder agreement for 1st and 2nd order themes was 83.3%
510 and 92.2%, respectively.

511 A total of 28 first order themes and six second order themes were developed and are
512 presented in Table 4. Table S9 presents all first order themes developed, the number of
513 times they were cited in the results sections of the studies included, the number of studies
514 citing it, and its association with the second order themes. In total 33 first order themes were
515 developed, however, as can be seen in table S9, five were only cited once and were
516 therefore not considered.

517

518 *Table 4 around here*

519

520 A comprehensive description of the themes is provided below. The themes Individual and
521 relational adjustment, Social adjustment and Fertility care perceptions and needs capture
522 changes across time in experiences and adjustment. The themes Acceptance, Meaning
523 making and Pursuit of new life-goal capture the psychological tasks patients engaged with
524 that were associated with positive adjustment in the aftermath of failed treatment.

525 *Individual and relational adjustment.* Participants described the period immediately after
526 ending treatment as of intense grief (pain, sadness and emptiness) and anger felt towards
527 'everything and everyone'. Grief endured in time and was lived in isolation. The grief
528 experience was different for women and men. For women it was very intense and
529 characterized by a sense of emptiness, meaningless, loss of control and self-blame. Women
530 tended to be open about their grief with their family and friends. Men felt pain, tried to
531 overcome grief by denying it and tended to be private in their suffering. Men were surprised
532 with the intense grief reactions of their (female) partners and felt it was their duty to be stoic
533 and supportive. However, they felt they lacked the knowledge to do this. In addition, most
534 participants reported that the treatment experience strengthened their partnership. However,
535 the sexual desire of many couples was affected during treatment and it did not recover once
536 treatment was over. Despite the initial difficulties and grief, as time passed participants

537 reported a sense of survival and personal and spiritual growth that was associated with
538 having undergone the treatment and the childlessness experience.

539 *Social adjustment.* Most participants experienced social isolation. Isolation was the result
540 of not meeting parenthood social norms and therefore being unable to share parenthood
541 experiences with peers. Men also felt isolated from family members, with whom they felt they
542 communicated less due to not having children. The absence of children was a loss
543 experienced by the whole family and raised concerns about not leaving a legacy to continue
544 the family bloodline and about loneliness in later life. Many women talked about how social
545 constructions and pressure for parenthood made it harder for them to accept their situation.
546 For instance, women's identities relied so strongly on parenthood that not having the desired
547 children made them doubt their femininity or feel abnormal. Some women felt the need to
548 show others they did everything they could to become parents to avoid social scrutiny.
549 Others talked about how it was difficult to escape society's expectations. Overall participants
550 felt that not meeting their parenthood goals hindered their relationship with their social
551 network. Despite the overall isolation, participants also described choosing to share their
552 struggles with a selected few close friends and work colleagues who provided them with
553 good emotional and instrumental support. Other people with infertility also provided them
554 with useful information. Finally, for women social isolation also resulted from active efforts to
555 avoid situations where children were present in order to escape suffering.

556 *Fertility care perceptions and needs.* Participants said that when all treatment options
557 were exhausted they felt abandoned by their clinic. They perceived a lack of support from the
558 clinic in both deciding if and when ending treatment and once this decision was made. They
559 expressed a need for psychosocial care or counselling to help them cope with the intense
560 grief they experienced, and for sexual counselling to help them overcome the sexual
561 difficulties that developed during treatment. Participants acknowledged the limitations of
562 reproductive medicine and this facilitated acceptance of their situation. Reaching acceptance
563 was associated with developing a positive outlook on ending treatment, for instance as
564 allowing participants to let go of their medical experience, as actively managing their child-
565 desire and as allowing others to also have an opportunity to achieve parenthood.

566 *Meaning making.* In the process of coming to terms with their unmet parenthood goals,
567 participants engaged in an intense re-evaluation effort whereby they tried to make sense of
568 their past efforts to achieve parenthood and they re-evaluated their life values and priorities
569 in search for a new identity and future in the absence of the desired children. Traditional
570 notions of marriage (e.g., marriages do not survive without children), femininity (e.g., women
571 are born to be mothers) and family (e.g., children are part of family life) hindered this
572 meaning making process. Therefore many participants questioned such beliefs and reflected
573 on the meaning of marriage and family without children. This critical approach to social

574 constructions of parenthood facilitated acceptance. Overall participants felt that meaning
575 making was associated with higher acceptance of one's unmet parenthood goals.

576 *Acceptance.* Immediately after finishing treatment participants maintained a strong hope
577 to have (more) biological children and felt unwilling or unable to accept their situation.
578 Acceptance was a process that unfolded over time because of the need to 'move on' with
579 life. Many patients differentiated rational from emotional acceptance and stated that although
580 rationally they accepted their situation, this was not synonymous with or followed by
581 emotional acceptance. Indeed, the hope to have the desired children could persist for many
582 years after treatment and for some women it only ended when they reached menopause, as
583 menstruation meant that a pregnancy was still possible. Acceptance was easier when
584 patients were convinced they did their best and explored all available treatment options,
585 when their efforts were acknowledge by their family and friends and met with empathy
586 instead of pressure for them to become parents. Acceptance was also easier when
587 participants felt they received good medical advice during treatment, when their prognosis
588 was clear and poor and when the reasons for treatment failure were identified. Acceptance
589 was associated with a change in the participants' view of the world. This translated in
590 recognizing their limits to control reality, in the development of a more realistic view of the
591 world or in increasingly valuing the 'good things' in life. Acceptance was also associated with
592 better adjustment. It translated in a sense of freedom from the infertility experience and hope
593 towards the future. This new state was described as of restored strength and agency, and
594 equilibrium with both the self and in the partnership. In contrast, the inability to accept their
595 situation was associated with maladjustment, in particular with continuous grief, feeling 'stuck
596 in life', low self-esteem and different avoidance strategies.

597 *Pursuit of new life-goals.* When ending treatment participants felt incapable of envisioning
598 themselves as anything else than parents. For most participants the need to move on with
599 their lives resulted from a desire to overcome the pain of grief and to reject self-pity and
600 continuous mourning. Coherently, the willingness to 'move on' was lower when there was a
601 stronger desire for children. Overall participants perceived that the needs to accept their
602 situation and 'move on' were interrelated. Participants' typical strategy was to invest in new
603 goals and activities that distracted them from their pain, compensated for their childlessness
604 status and boosted their self-esteem. Despite desiring to 'move on', many participants did not
605 know how to do this and expressed that the process required an active effort to look into the
606 future, which implied a confrontation with later life stages and their lack of legacy.
607 Participants talked about many different ways of finding new fulfilling life goals and activities
608 and these included caring for other people (e.g., family members) and pets, supporting
609 friends with infertility and advocating for the rights of other infertile people, travelling and
610 focusing on their career and, when full acceptance was achieved, some individuals even

611 refocused on caring for other children (e.g., siblings). Overall participants felt that the pursuit
612 of new life-goals was associated with higher acceptance of their unmet parenthood goals.

613

614

Discussion

615 Findings from this mixed-methods systematic review show that people who do not
616 manage to conceive with fertility treatment experience worse mental-health (i.e., more
617 psychopathologic symptoms) and wellbeing (lower positive functioning and life satisfaction)
618 than those who conceive. Positive adjustment in this context seems to be associated with a
619 progressive acceptance of the loss; making meaning of past efforts to conceive and the
620 present situation; and pursuing new life goals or activities. Individuals who engage with these
621 three psychological tasks tend to report a sense of personal growth and to develop a positive
622 outlook on ending treatment and renewed views of the world. The results reported suggest
623 that the risk for maladjustment varies according to individual, social and treatment related
624 factors. Overall the data indicate that the post treatment period is worthy of clinical attention
625 and reinforce advice for health professionals to support individuals during this period.

626 Long-term adjustment after failed fertility treatment is an emergent research topic within
627 reproductive psychology. Only 18 studies could be identified for inclusion with an even split
628 between quantitative and qualitative research. An examination of the papers excluded (see
629 Figure 1) indicates that researchers tended to focus on the first 12 months following
630 treatment (only capturing short term reactions), did not report on time since treatment,
631 focused on topics either than adjustment, or, if they focused on adjustment, did not use a
632 control group. From the included studies only two reported on correlates or predictors of
633 adjustment (Gameiro et al. 2016, Verhaak et al. 2007) making it impossible to quantitatively
634 investigate risk factors. In sum, research on this topic is still at a descriptive state that needs
635 to be moved towards an explanatory theory-driven approach. This mixed-methods review is
636 timely in that it provides the evidence base for the development of testable hypotheses
637 organized in a comprehensive theoretical model.

638 Results from the meta-analysis show that individuals who do not manage to conceive with
639 fertility treatment report significantly worse mental-health (medium effect sizes) and wellbeing
640 (small to medium effect sizes) than those who do. Moderation analyses focusing on the type
641 of control group and percentage of children in the failed treatment group suggest that the
642 poorer adjustment of the failed group is better explained by their inability to meet their
643 parenthood goals than their childless status. Indeed, group differences in mental-health were
644 larger when based on the treatment outcome than on parenthood status (-0.604 versus -
645 0.108) and the existence of children in the failed treatment group did not prove to be a
646 significant moderator for mental-health nor wellbeing. These data suggests that what is
647 associated with worse adjustment is having less children than desired or, in other words, not

648 meeting ones parenthood goals. Recent research shows that both the population of people
649 with undesired childlessness and fewer children than desired are increasing as a result of
650 parenthood delay (Schmidt et al. 2012).

651 Contrary to our hypothesis, group differences in mental-health and wellbeing did not
652 subside within the 20 years time period surveyed. However, this result needs to be carefully
653 considered because it may be explained by a methodological limitation in the
654 operationalization of time since treatment. Indeed, seven out of the nine studies included
655 provided a range for time since last treatment (instead of a specific time or average) and this
656 could span several years. In these cases we had to use the mean and this is likely to have
657 obscured associations.

658 Findings from the qualitative review indicate that positive adjustment is dependent on
659 individuals accepting and making meaning of their unmet parenthood goals and pursuing
660 new life-goals. Individuals perceived these as three separate but inter-dependent
661 psychological tasks. Acceptance was portrayed as a process (and not an outcome). It
662 appears to involve the emotional processing of one's unmet parenthood goals. According to
663 psychological theories, this implies the activation and restructuring of maladaptive fear
664 structures, exposure and habituation to the situation and regulation of the negative affect it
665 elicits (Park 2010). Therefore, acceptance may be fostered by emotional approach coping to
666 the loss (Boelen et al. 2006, Stanton et al. 1994) so that, in accordance with grief models, its
667 integration in autobiographical knowledge is achieved (Boelen et al. 2006). However, unmet
668 parenthood goals can be an ambiguous loss because the chances of achieving parenthood
669 are rarely completely null. This may preclude the integration of the loss. Indeed, our
670 qualitative data showed that acceptance was easier when chances to conceive were lower
671 (poor prognosis, clear advice to stop treatment from fertility team, reasons for failure
672 identified), or in other words, when the loss was perceived as definitive.

673 Meaning making seems to reflect an adaptive cognitive processing of the situation. The
674 literature about adaptation to stressful life events or trauma (e.g.; Park 2010, Taylor 1983)
675 considers meaning making as a critical task for adjustment and states that individuals will
676 always engage in it in order to restore a sense of control and predictability over their lives
677 (Kelley and Michela 1980). Our results seem to be consistent with this literature in that
678 patients perceived meaning making and acceptance to be related and in that acceptance
679 was associated with new views of the world and redefinition of priorities in life (Park 2010).
680 Grief theorists also claim that such cognitive processing needs to address dysfunctional
681 beliefs associated with the loss (Boelen et al. 2006). For instance, individuals talked about
682 guilt related with ending treatment and concerns about their role in their family. Previous
683 research also highlighted concerns about the impact of not achieving parenthood on the
684 partnership and one's ability to endure the related grief (Boivin et al. 2005). In this context,

685 self-blaming and catastrophizing were shown to be negatively associated with adjustment
686 (Kraaij et al. 2009). On the contrary, positive reappraisal coping may assist meaning making
687 and was associated with positive adjustment (Kraaij et al. 2009, Peterson et al. 2009).

688 Finally, results suggest that the pursuit of new life goals is associated with higher
689 acceptance of the unmet parenthood goals and, in the long-term, better adjustment.
690 Individuals claimed that pursuing new life goals required an active effort from their part.
691 According to the dual process model of grief, this can be regarded as an effort to process the
692 implications of the loss (Stroebe and Schut 1999) by finding new purpose(s) for living and
693 regaining a sense of agency. A recently published meta-analysis showed that, in the context
694 of a parenthood blockage, reengagement in new life goals is associated with better wellbeing
695 (i.e., higher positive mood; Mesquita da Silva et al. 2016). Our results support these data, but
696 also show that engaging with new life goals is harder for individuals who highly value
697 parenthood or perceive a lack of other meaningful goals to pursuit (Thoits 1992). Our data
698 also show that individuals start by pursuing other goals just as a distraction from the suffering
699 of not achieving their main goal of parenthood, but that they end up perceiving benefits from
700 this. These results are consistent with literature showing that pursuing new goals is adaptive
701 even when individuals have not completely disengaged from parenthood (Wrosch et al.
702 2003).

703 Another important finding was how the unmet parenthood goals affected individuals'
704 social relationships and how their social context influenced their adjustment process. This is
705 not surprising as it is well known that the socio-cultural context has a strong influence in
706 shaping the experience of infertility and childlessness of both women and men (Greil et al.
707 2011, Martins et al. 2016). Social isolation was a common theme in the data, either resulting
708 from less empathic reactions from the social network or from self-avoidance of that social
709 network, when it implied contact with children. Social support is a consistent protective factor
710 in the context of infertility and its treatment (Martins et al. 2016, Rockliff et al. 2014). Our
711 data was no different in this regard, but also showed that the social context could influence
712 adjustment via other routes than support, more specifically via social norms (i.e., social
713 pressure for parenthood) and prevalent representations of parenthood, marriage and
714 femininity. Overall, the pervasiveness of social and cultural first order themes suggests that
715 psychosocial care needs to include a thorough assessment of the social context and provide
716 individuals with strategies to cope with it.

717

718 **Strengths and limitations**

719 The strengths of this mixed-methods review were the systematic review of almost 40
720 years of research on adjustment after failed fertility treatment, which yielded 18 studies from
721 ten countries sampling adjustment experiences of 2545 patients. Data were independently

722 extracted and quality evaluations and analyses were made according to a-priori defined and
723 rigorous protocols in order to minimize the risk of bias. Another strength was the inclusion of
724 quantitative and qualitative research to answer different research questions, allowing for a
725 more comprehensive picture of adjustment to emerge. The primary research was of
726 moderate to high quality. In quantitative studies quality was due to the fact that most studies
727 had a representative sample of the population, used valid and reliable outcome measures
728 and had enough power to detect significant differences. In qualitative studies the quality was
729 due to the adequacy of the design, recruitment strategy and data collection method used.
730 However, the quantitative studies did not focus on investigating risk factors for
731 maladjustment and used heterogeneous samples of individuals in terms of time since
732 treatment and parenthood status. It was also not totally clear if those individuals who did not
733 reach parenthood via treatment were still pursuing it, for instance by doing more treatment at
734 different clinics or by choosing to adopt. These data, together with previous research (e.g.,
735 Gameiro et al. 2014, Wischmann et al. 2012), suggest that the larger the proportion of the
736 sample still pursuing parenthood the worse adjustment will be. The main problem of the
737 qualitative data was that, due to the nature of qualitative research, the data extracted from
738 the papers were interpretations that other researchers made of patients' interpretations of
739 their experiences. Another problem was that the goals of the qualitative studies varied
740 slightly, for instance one study focused only on the perceived gains of doing fertility treatment
741 (Lee et al. 2009). This might have affected the prevalence of the emergent themes.

742 Despite these limitations, overall the results from the quantitative and qualitative review
743 were consistent and its integration provided a coherent picture of adjustment after failed
744 treatment. The only inconsistency detected was that qualitative data provided a more positive
745 perspective on adjustment over time than the quantitative data. However, we explained that
746 the quantitative data might not be reliable. Furthermore, it should be noted that the
747 quantitative data tapped into hedonic wellbeing, which is the extent to which individuals are
748 'feeling well', and the qualitative data also captured eudaimonic wellbeing, which is the extent
749 to which individuals are 'doing well' in terms of purpose, meaning and fulfilment in life (Ryan
750 and Deci 2001). By analysing both types of data we achieved a more nuanced view of
751 wellbeing, which can explain the discrepancy observed.

752

753

Conclusions

754 Based on the data reported we developed a comprehensive model to explain adjustment
755 to unmet parenthood goals, labelled the Three Tasks Model of Adjustment to Unmet
756 Parenthood Goals and presented in Figure 3. The model predicts that, in the face of unmet
757 parenthood goals, individuals able to accept their situation, make meaning of their
758 experience and pursue new life goals will adjust better than those who do not engage with

759 these psychological tasks. These three main predictions are consistent with knowledge from
760 other theories previously used to explain adjustment after failed treatment and general
761 theories of adjustment to stressful life events. The Three Tasks Model of Adjustment to
762 Unmet Parenthood Goals also predicts that specific variables may influence adjustment,
763 either directly (e.g., women are more likely to present worse adjustment), by impacting on the
764 individual's ability to perform the three psychosocial tasks (e.g., one is less likely to pursue
765 new goals if they do not find alternative meaningful goals), or by moderating the relationship
766 between the three psychological tasks and adjustment (e.g., pursuit of new life goals is more
767 likely to lead to better adjustment when one is supported by their network than when is not
768 supported). The variables identified were, at the individual level, gender, importance of
769 parenthood and availability of alternative life goals; at the social level, social support, social
770 representations of parenthood and parenthood social norms; and at the treatment level,
771 prognosis, perceived quality of medical advice, reasons for failure identified and treatment
772 options exhausted.

773 In this review we considered two adjustment outcomes: mental health and wellbeing. The
774 meta-analysis showed that these are sensitive measures in this context and should therefore
775 continue to be used in future research. The qualitative data suggests that patients assess
776 their adjustment not only in terms of how they feel (hedonic wellbeing, e.g. intense grief,
777 anger) but also in terms of how they think they are realizing their human potential
778 (eudaimonic wellbeing, e.g. resilience and personal and spiritual growth; Ryff 1995). Future
779 research could consider using outcomes that tap into eudaimonic wellbeing. This seems
780 particularly important in this context because the pursuit and realisation of intrinsic goals
781 seems to be more strongly related with eudaimonic than hedonic wellbeing (Ryan and Deci
782 2001). Examples of eudaimonic outcomes would be self-acceptance (positive evaluations on
783 oneself and one's past life, personal growth (sense of continued growth and development as
784 a person) or purpose in life (the belief that one's life is purposeful and meaningful (Ryff and
785 Keyes 1995).

786 In conclusion, this mixed-methods review offers compelling evidence for the need to
787 provide psychosocial care directed at helping individuals relinquishing their parenthood
788 goals. Patients themselves recognize the need for psychosocial care during this period and
789 express frustration at feeling abandoned by their clinic. The Three Tasks Model of
790 Adjustment to Unmet Parenthood Goals offers comprehensive guidance on the therapeutic
791 mechanisms that seem to underlie positive adjustment. The model was developed based on
792 the experiences of patients who experienced failed fertility treatment, but there is nothing to
793 suggest that it cannot be applied to everyone who is confronted with the loss of their
794 parenthood goals, regardless of the pathway that led to it. Future research should now test
795 the model in these different contexts. This can be done by conducting prospective cohort

796 studies to test the model predictions. Another way to test the model is by developing and
797 testing psychosocial interventions that are based on its three main hypothesis, in other
798 words, interventions designed to engage individuals with acceptance, meaning making and
799 pursuit of new goals. An important question in this context is how such specialized care can
800 reach individuals who are already outside the reproductive healthcare system. The ESHRE
801 guideline argues that this is the responsibility of fertility clinics (Gameiro et al. 2015). We
802 concur that specialized expertise is needed to develop and test effective interventions. A
803 sensible approach would be to develop self-help interventions that individuals could access
804 via multiple outlets (the most obvious one being the internet) instead of having to go back to
805 their fertility clinics. Another crucial approach is to promote knowledge transfer about the
806 topic so that primary care physicians and mental-health professionals are aware of the
807 deleterious impact of unmet parenthood goals on wellbeing and of how it can be addressed.

808

809 **Author's roles**

810 S.G. did data extraction, critical appraisal, data analysis and interpretation and writing of
811 the report. A.F. did data extraction, critical appraisal, data analysis and interpretation. All
812 authors approved the final version for submission.

813

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817

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821

822 **Conflict of interest**

823 There are no conflicts of interest.

824

825 (Hammarberg et al. 2001, Johansson and Berg 2004, Lee et al. 2009, McCarthy 2008, Su
826 and Chen 2006, Sydsjö et al. 2015, Throsby 2001)

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830

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Table 1. Characteristics of the nine included quantitative studies

Authors, year Country	Fertility treatment	Failed treatment group	Control group	Existence of children in failed treatment group (YES, NO) ^a	Years since last treatment cycle	Design	Response /attrition rate	Quality	Mental- health ^b	Wellbeing ^b
Gameiro et al 2014 The Netherlands	Fertility drugs/ IUI/ AI/ IVF/ ICSI/ gamete donation	1493 women	5655 women with children ^b	NO	range 11-17	Cross-sectional	60.4%	High	✓	✗
Hammarberg et al 2001 Australia	IVF/ ET/ GIFT	65 women	51 women successful treatment	YES	range 2.5-3.5	Cross-sectional	55%	Moderate	✗	✓
Johansson et al 2010 Sweden	IVF/ ET/ ICSI	149 women + 121 men	118 women + 93 men with children	YES	range 4-5.5	Cross-sectional	67.5%	Moderate	✓	✓
Kuivasaari-Pirinen et al 2014 Finland	IVF/ ICSI	209 women	296 women successful treatment	YES	range 1.3-11.7	Longitudinal	100% / 54.7%	Moderate	✗	✓
Leiblum et al 1998 USA	IVF	18 women	41 women successful treatment	NO	range 2-13	Cross-sectional	31%	Moderate	✓	✓
Sydsjö et al 2015 Sweden	IVF	62 men	230 men with children	NO	20	Cross-sectional	66.5%	Moderate	✓	✗
Verhaak et al 2007 The Netherlands	IVF/ ICSI	39 women	68 women successful treatment	NO	range 3-5	Longitudinal	84% / 78%	High	✓	✗
Weaver et al 1997 UK	IVF/ GIFT	21 couples	20 couples successful treatment	YES	range 1.25-2.25	Cross-sectional	95%	Moderate	✓	✓
Wischmann et al 2012 Germany	IUI / IVF/ ICSI	40 couples	91 couples successful treatment	NO	10 (since first consultation)	Cross-sectional	35.7%	Moderate	✗	✓

Legend. SC = spontaneous conception; IVF = in-vitro fertilisation; ICSI = intra-cytoplasmic sperm injection; FET = frozen thawed embryo transfer cycle; IUI = intrauterine insemination; GIFT = gamete intrafallopian transfer; AI = artificial insemination; ET = embryo transfer; NR = not reported; ^a children could be adopted or conceived spontaneously or with previous fertility treatment; ^b ✓ = reported; ✗ = not reported. Note: 180 (2.5%) patients who participated in the Gameiro et al 2014 study also participated in the Verhaak et al 2007. Due to the extremely low sample overlap we still included the two studies.

Table 2. Characteristics of the nine included qualitative studies

Author, year Country	Goal	Failed treatment group	% with children	Design	Years since treatment	Data collection method	Analytical method	Quality
Boden 2007 UK	Extend the understanding of how women and their partners experience infertility and come to terms with their childlessness	18 couples + 15 women	NR	Cross- sectional	5	Interviews	Thematic analysis	High
Daniluk 2001 Canada	Understand how couples make sense of their infertility and reconstruct their lives when faced with the permanence of their biological childlessness	37 couples	46	Longitudinal	1, 1.83 & 2.66	Semi-structured interviews	Phenomenological analysis	High
Johansson & Berg 2004 Sweden	Describe women's experiences of ongoing childlessness 2 years after the end of IVF treatment	8 women	13	Cross- sectional	2	Unstructured interviews	Phenomenological analysis	Moderate
Lee <i>et al</i> 2009 China	Provide an in-depth description of the gains perceived by Chinese men and women and how they re-constructed their lives after unsuccessful IVF treatment	4 couples (4 women + 4 men) + 6 women	36	Cross- sectional	range 0.5 – 3	Semi-structured interviews (joint and individual)	Grounded Theory	High
McCarthy 2008 USA	Understand the lived experience of infertility for women in the aftermath of unsuccessful medical treatment	22 women	32	Cross- sectional	3.9, SD 3.2	Interviews	Hermeneutic– phenomenology	High
Su & Chen 2006 Taiwan	Explore the lived experiences of infertile women who terminated treatment after IVF failure	24 women	NR	Cross- sectional	1.33, SD 0.33 range 1-1.92	Telephone interviews	Phenomenological analysis	High
Throsby 2001 UK	Identify the factors which inform the decision to end treatment; consider the ways in which the unsuccessful engagement with IVF marked both the experience of infertility and the participants' own perceptions of that technology; explore the ways in which those feelings might change over time and the influence they might have on subsequent choices	13 couples + 15 women	54	Cross- sectional	2	Interviews	Discourse analysis	High
Volgsten <i>et al</i> 2010 Sweden	Explore the experience of undergoing unsuccessful in vitro fertilization (IVF) treatment and of remaining childless 3 years after IVF in both women and men	7 couples + 3 women + 2 men	21	Cross- sectional	3.17	Semi-structured interviews	Content analysis	High
Wirtberg <i>et al</i> 2007 Sweden	Obtain an increased knowledge and deeper insight into the long-lasting effects of, and coping with, involuntary childlessness for a group of women who had sought help for infertility and had completed infertility treatment over 20 years before	14 women	0	Cross- sectional	20	Semi-structured interviews	NR	Moderate

Legend. IVF = In Vitro Fertilization; NR = not reported.

Table 3. Subgroup and meta-regression analyses of mean differences between the failed treatment and control groups for mental-health and wellbeing.

Mental-health					Wellbeing					
Subgroup analysis	<i>k</i>	Effect size	95% CI LL	95% CI UL	χ^2	<i>k</i>	Effect size	95% CI LL	95% CI UL	χ^2
Comparison groups					12.534***					NA
Based on treatment outcome (failed, successful)										
Based on parenthood status (no children, children)										
No	4	-0.648	-0.828	-0.467		5	-0.324	-0.454	-0.193	
Yes	2	-0.108	-0.168	-0.048		0				
Existence of children in failed treatment group					0.050					0.679
No	5	-0.484	-0.803	-0.165		2	-0.228	-0.491	0.036	
Yes	1	-0.589	-1.457	0.279		3	-0.355	-0.505	-0.205	
Quality					1.132					NA
Moderate	4	-0.608	-0.953	-0.263		5	-0.324	-0.454	-0.193	
High	2	-0.323	-0.719	0.073		0				
Meta-regression		Coefficient	95% CI LL	95% CI UL	z		Coefficient	95% CI LL	95% CI UL	z
Years since treatment	6	0.025	-0.003	0.052	1.777	5	0.055	-0.008	.117	1.712

Legend. *P<0.05, **P<0.01, ***P<0.001, ART = assisted reproductive techniques, k=number of studies, CI = confidence intervals, LL = lower limit UL = upper limit, NA = not applicable as there were not enough studies in the group, bold indicates P<0.05

Table 4. First and second order themes developed to describe patients' experiences after failed fertility treatment. Second order themes are presented in bold with a grey background. For each of the second order themes the associated first order themes are listed below.

Individual and relational adjustment	Social adjustment	Fertility care perceptions and needs
<p><u>Immediately after ending treatment</u></p> <ul style="list-style-type: none"> • Intense grief (especially for women) • Anger directed at 'everything & everyone' • Treatment strengthens partnership • Men stoic & supportive of their partner • Sexual difficulties <p><u>As time since treatment passed</u></p> <ul style="list-style-type: none"> • Resilience & personal & spiritual growth 	<ul style="list-style-type: none"> • Social isolation • Parenthood loss hinders partner and social relationships • Social representations of parenthood hinder adjustment • Support from selected family members & friends • Social avoidance 	<p><u>Immediately after ending treatment</u></p> <ul style="list-style-type: none"> • Feeling abandoned\lack of support from clinic • Need for psychosocial & sexual care/counselling • Acknowledgement of reproductive medicine limitations <p><u>As time since treatment passed</u></p> <ul style="list-style-type: none"> • Positive outlook on ending treatment
Meaning making	Acceptance	Pursuit of new life-goals
<ul style="list-style-type: none"> • Need to find meaning in life (past efforts, new identity & future) • Questioning of traditional notions of marriage, family... in light of parenthood loss • Re-evaluation of life values & priorities • Acceptance and meaning making are interdependent 	<p><u>Immediately after ending treatment</u></p> <ul style="list-style-type: none"> • Inability/unwillingness to accept childlessness <p><u>As time since treatment passed</u></p> <ul style="list-style-type: none"> • Acceptance easier when... [all options explored, efforts acknowledged, no pressure for parenthood, good medical advice, poor prognosis, reasons for failure identified] • Acceptance associated with new views of the world • Non-acceptance associated with worse adjustment • Acceptance associated with better adjustment 	<ul style="list-style-type: none"> • New fulfilling goals/activities include... [adoption, caring for other children (e.g., siblings) or pets, supporting & advocating for the rights of the infertile, travelling, career/professional development] • 'Moving on' requires active effort • Need to 'move on' with life • Acceptance and pursuit of new life-goals are interdependent.

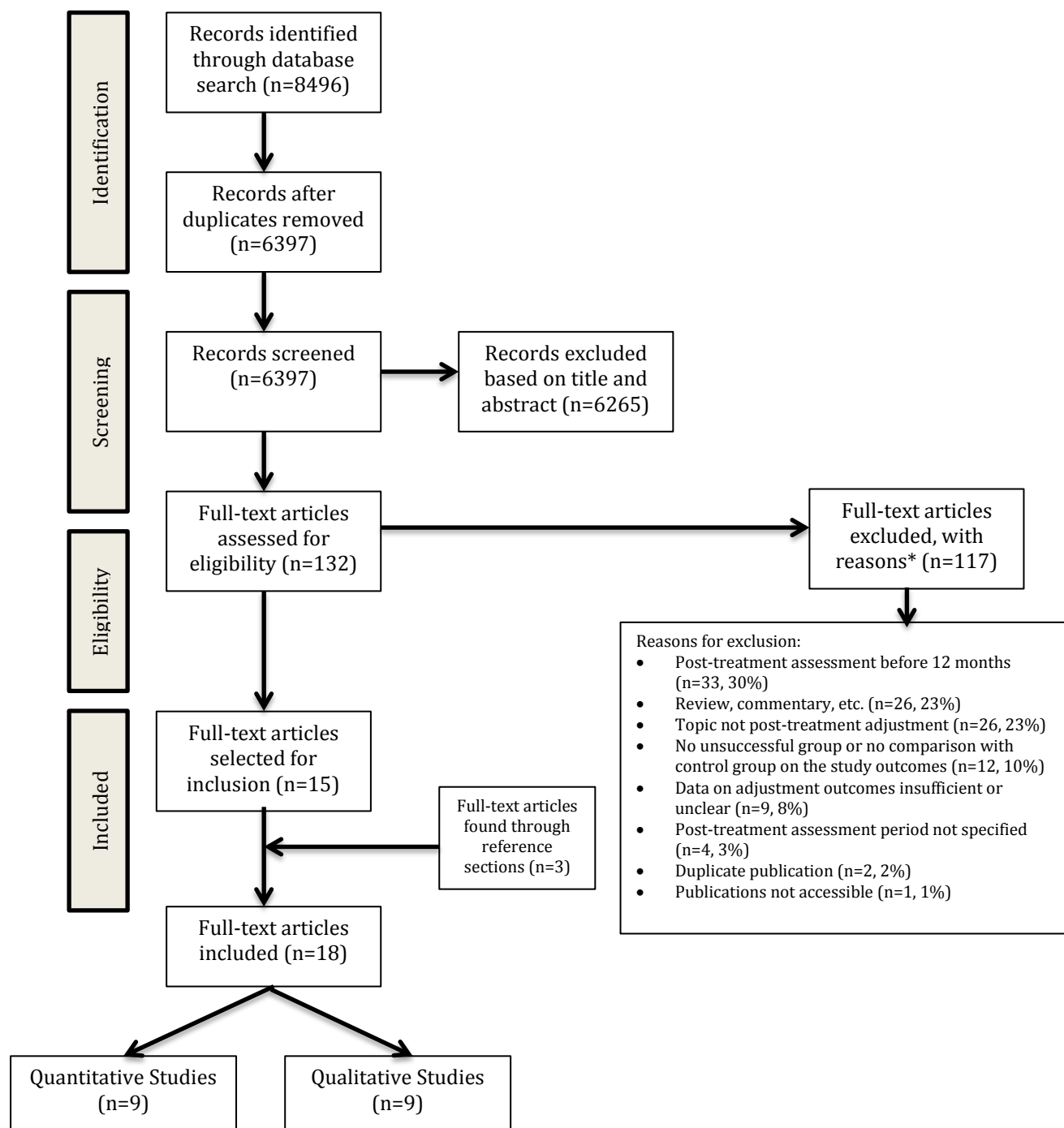


Figure 1. Decision flow chart for identified studies. * For detailed exclusion strategy see Table S2 of the supplementary material.

Mental-health

Study names	Statistics for each study						Hedges's g and 95% CI				
	Hedges's g	Standard error	Lower limit	Upper limit	Z-Value	p-Value	-2.00	-1.00	0.00	1.00	2.00
Gameiro et al 2014	-0.093	0.031	-0.155	-0.032	-2.968	0.003			+		
Johanssen et al 2010	-0.742	0.186	-1.107	-0.377	-3.985	0.000		+			
Leiblum et al 1998	-0.753	0.287	-1.317	-0.190	-2.620	0.009		+			
Syydsjo et al 2011	-0.415	0.144	-0.696	-0.133	-2.884	0.004		+			
Verhaak et al 2007	-0.596	0.123	-0.838	-0.355	-4.833	0.000		+			
Weaver et al 1997	-0.589	0.299	-1.175	-0.004	-1.972	0.049		+			
	-0.496	0.151	-0.791	-0.200	-3.283	0.001		+			

Wellbeing

Study name	Statistics for each study						Hedges's g and 95% CI				
	Hedges's g	Standard error	Lower limit	Upper limit	Z-Value	p-Value	-2.00	-1.00	0.00	1.00	2.00
Hammarberg et al 2001	-0.502	0.189	-0.872	-0.132	-2.658	0.008			+		
Johansson et al 2010	-0.355	0.183	-0.715	0.004	-1.939	0.052			+		
Kuivasaari-Pirinen et al	-0.300	0.091	-0.478	-0.122	-3.305	0.001			+		
Leiblum et al 1998	-1.168	0.299	-1.754	-0.582	-3.907	0.000		+			
Weaver et al 1997	-0.484	0.222	-0.919	-0.048	-2.177	0.029			+		
Wischmann et al 2012	-0.080	0.197	-0.466	0.307	-0.404	0.686			+		
	-0.415	0.108	-0.627	-0.203	-3.840	0.000			+		

Figure 2. Standardized mean differences (Hedge's g, Standard Error (SE), 95% Confidence Intervals (CIs), Z value and P value) between failed treatment and control groups for mental-health and wellbeing. Negative Hedge's values indicate worse adjustment for the failed treatment group than the control group.

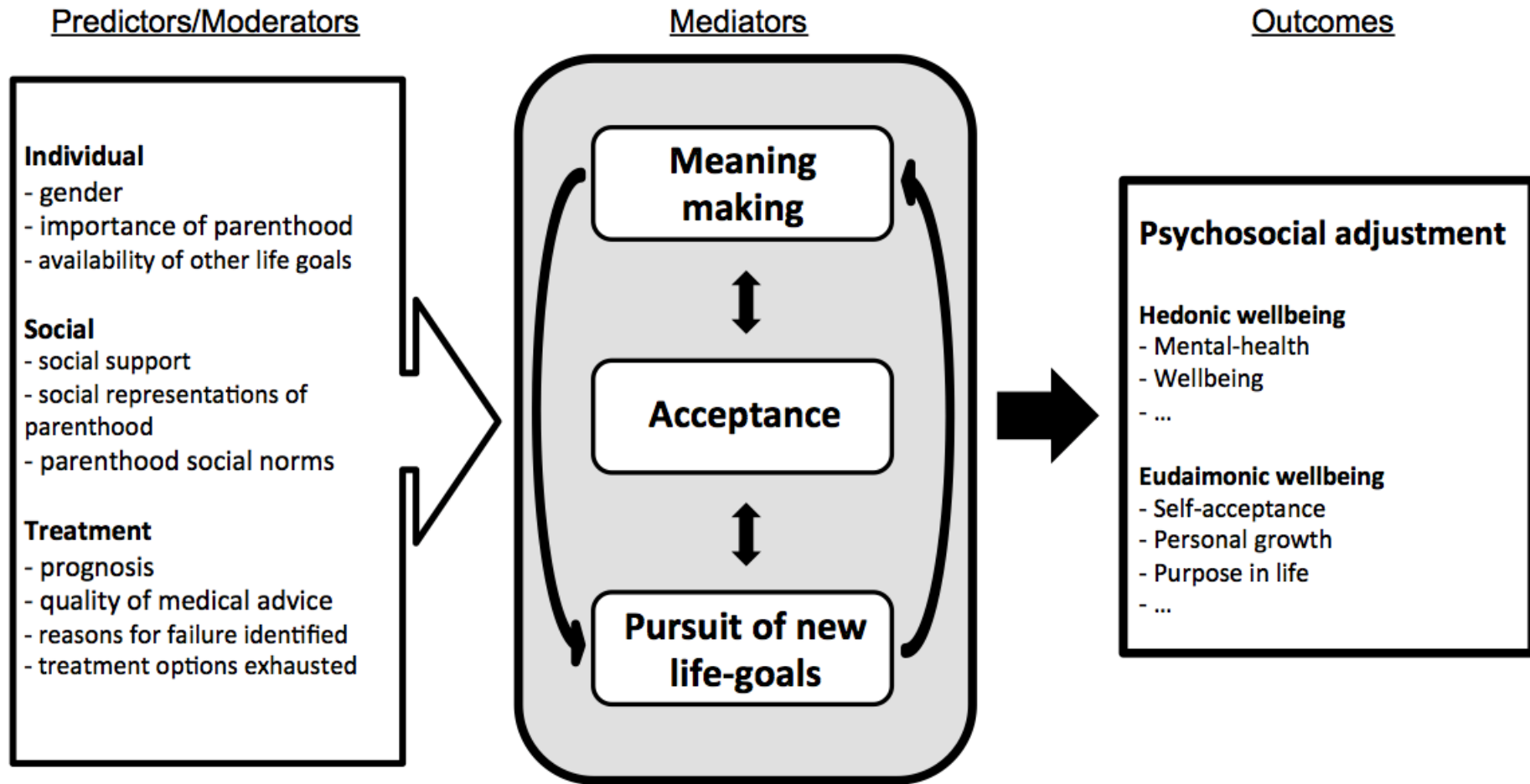


Figure 3. A schematic representation of the Three Tasks Model of Adjustment to Unmet Parenthood Goals