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Mental health in women 20-23 years after IVF treatment: A cross-sectional study

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ABSTRACT

Objective: To assess self-perceived mental health in women treated with in vitro fertilization (IVF) 20-23 years previously, while comparing them to controls, and to determine any differences in mental health between those who had given birth, those who had adopted a child, those who had given birth and adopted a child and those who remained childless.

Design: Cross-sectional study.

Setting: A Center of Reproductive Medicine (RMC) at a Swedish University hospital

Participants: 520 women who had undergone at least one IVF cycle at the University Hospital in Linköping between 1986 and 1989. 504 of the 520 women (97%) were eligible for follow-up. While 34 women declined, 93 percent (n=470) agreed to participate. The reference group consisted of 150 women from the Swedish population included in a study that was used to validate the SCL-90.

Interventions: Follow-up was conducted in 2008-2009. The Symptom Check List – 90 (SCL-90) was used to measure the women's self-perceived mental health and a questionnaire specific for this study was used to retain demographic information.

Outcome measures: The SCL-90 assesses 9 primary dimensions; somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism. There is also a global index of distress.

Results: Women who had previously undergone IVF treatment were at increased risk of symptoms of depression (p=.017), obsessive compulsion (p=.02) and somatization (p=<.001) 20 years later when compared to a control group. In addition, the women who have remained childless are at increased risk of suffering symptoms of depression (p=.009) and phobic anxiety (p=.017).

Conclusion: In general, the mental health in women who have undergone IVF treatment 20-23 years previously appears to be good. However, women who remain childless and/or

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without partner after unsuccessful infertility treatment, constitute a vulnerable group even later on in life. These women may be in need of follow-up.

Strengths and limitations of the study

- This is one of few studies on the long-term mental health of women who have been treated with IVF
- The follow-up period is exceptionally long at 20-23 years
- The participation rate was very high at ninety-three percent (n=470)
- Unfortunately, possible confounding factors such as educational level and life events could not be controlled for

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INTRODUCTION

Infertility, its investigations and treatment can cause psychological distress[1] , such as symptoms of anxiety and depression[2-4]. The infertility treatment itself further adds to the strain created by the infertility [5, 6]. Psychological wellbeing in women after in vitro fertilization (IVF) treatment is dependent upon treatment results. Studies examining psychological wellbeing up to ten years after IVF treatment have found that women who remain childless are at increased risk of anxiety,[6, 7] depression,[,6,7, 8] and stress[8] and have a lower sense of coherence,[7] self-esteem [8] and satisfaction with life [8,9] than those who had given birth after treatment. Also, women who give birth after treatment are at decreased risk of hospitalization due to psychiatric disorders [10, 11] and show a more positive long-term emotional status. [4] Gameiro et al. (2014) showed that women who had undergone infertility treatment 11-17 years previously suffered more mental health problems, when compared to the general population, and that a sustained child-wish negatively affected mental health.[12] Meanwhile, studies have shown that most women come to terms with their parenthood goals.[12-14] This shows that reorientation and coping after unsuccessful IVF treatment is important [4,15-17] and that couples may be in need of counselling after unsuccessful IVF treatment to resolve the grieving process.[18] Twenty years after infertility treatment the relationship quality in the couples who have previously undergone infertility treatment is good [19] although a qualitative study on 14 women showed that they still suffered negative effects of the infertility which were especially great when the women were going through the grandparent phase.[20]

Thus, there are only a few studies on the mental health of women who have been treated with IVF from a long-term perspective. It is still unclear what effects infertility and its treatment has on women in a long-term perspective.

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The aim of the present study was to assess self-perceived mental health in a group of women treated with IVF 20-23 years earlier. Secondly, we wanted to study possible differences in mental health between the four groups; those who had given birth, those who had adopted a child, those who had given birth and adopted a child and those who remained childless.

METHOD

Subjects

All women (n=520) who had received at least one IVF treatment cycle at the Center of Reproductive Medicine, University Hospital in Linkoping between 1986 and 1989 were, in 2008 to 2009, sent an introductory letter asking them to participate in the study. Six of the women were deceased and ten women never received the letter, thus 504 out of 520 (97%) women were eligible for follow-up. Out of these, ten women returned the letter declining participation and 24 women did not answer. Thus, a total of 470 out of the 504 (93%) women eligible for follow-up agreed to participate. Out of the ninety-three percent (n=470) of the women who agreed to participate 55.1% (n=259) had biological children, 19.4% (n=91) had adoptive children, 5.3% (n=25) had both biological and adoptive children and 20.2% (n=95) had remained childless. As a reference group we used score mean values for 150 women of the general Swedish population. This data was derived from a population based study, through which the SCL-90 was validated, of women older than 40 years of age.[21, 22]

Treatment procedures 1986-1989

The couples were given three or more publically funded IVF treatments during this time period. Some of the couples might have had at least one child before entering treatment

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during this period. The upper age limit for the women was 38 years at the time of treatment. The waiting time from acceptance to treatment was approximately three years.

Outcome measures

The Symptom Check List – 90 (SCL-90) was used to measure the women's self-perceived mental health during the past week. The SCL-90 is an extensively used, multidimensional psychological status symptom inventory consisting of 90 items.[13,14] It is an objective method for symptom assessment requiring individuals to rate their psychopathological problems and symptoms. These symptoms are then used to compute scores for depression and anxiety. The scale is a five-point Likert scale ranging from "not at all" (0) to "extremely" (4). The SCL-90 assesses 9 primary dimensions; somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. There is also a global index of distress that can be used as a summary dimension. The cut off score on the SCL-90 of < 70 was used as an indicator of mental health. [21]

Demographics

Age, employment status, marital status, same/different partner since time of IVF treatment, number of children (biological and adopted), number of miscarriages and number of IVF treatments were assessed through a questionnaire specific for this study. Those with same/different partner since time of IVF treatment thus constitute a subgroup to those who were married/cohabiting.

Statistics

Two sided Chi2-tests were used to analyze differences between the subgroups in regard to background variables and self-perceived mental health. Student's t-test, also two sided, was

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used to compare mean scores between all women who had received IVF treatment and those in the reference group. Effect sizes using Cohen's distance was calculated in order to evaluate the magnitude of the differences of the mean scores between IVF treated women and women in the reference group. P-values <.05 was considered significant. All statistical analyses were performed using IBM SPSS version 19 (IBM Corporation, Armonk, NY).

RESULTS

Demographics

The distribution of demographics across the three groups is shown in Table I. The majority of the women were older than 45 years at the time of follow-up. Those who had remained childless and those who had adopted children were significantly (p=<.001) more likely to be aged over 45 years than were those with biological children. While 41.5% (n=39) of the women without children were divorced or separated the corresponding number for the women with biological children were 7.0% (n=18) (p=<.001). Among those with adopted children, all women were married or cohabiting. Also, those with adopted children were the most likely to still be living with the same partner as they were at the time of IVF treatment (98.9%; n=90). Those without children (90%; n=54) who were cohabiting or married were more likely than those with biological children (70.6%; n=175) to have remained with the same partner (p=<.001) (Table I).

The women had on average been through 2.7 (range=1-10) IVF cycles and 189 of the women had experienced 1-10 miscarriages (mean=1.9).

Self-perceived mental health

The women's own perceived mental health is displayed in table II. Women who had biological or adoptive children were less likely to experience symptoms of phobic anxiety

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than who had remained childless (p=.017) (Table II). Also, women who had biological children were also significantly less likely than women who had remained childless to experience symptoms of depression (p=.009). Women, who were separated, lived alone or who were unemployed showed more signs of depression, anxiety and obsessive-compulsive problems compared to women who were married and were gainfully employed. Women who were over 45 years of age also had more symptoms of mental illness. Women who had changed partner since the time of IVF had more obsessive-compulsive symptoms compared to women who still had the same partner but there were no other differences between these two groups (Table II).

In regard to "Global severity index" and "Positive symptom total" the women who had experienced infertility within the couple and who had been through a number of IVF treatments 20-23 years earlier showed the same pattern as the age-matched reference group (Table III). Only on the "Positive symptom distress index" did the IVF group have a higher score indicating that these women had reported experiencing more intense symptoms. In regard to the specific symptoms, the women who had previously undergone IVF treatment were at increased risk of depressive and obsessive-compulsive symptoms as well as having increased scores for somatization (Table III).

DISCUSSION

Principal findings

The majority of the women who had been treated with IVF 20-23 years previously reported few mental health problems. However, women who had remained childless 20 years after infertility treatment reported negative psychological consequences to a greater degree than those who had since become mothers. Childless women were more prone to symptoms of

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depression than were those with biological children and to symptoms of phobic anxiety than were the women who had biological or adopted children. Women who had remained childless were more likely to be separated or divorced, a group which to a greater degree reported suffering from depressive, anxiety and obsessive-compulsive symptoms. When all women who had undergone IVF treatment were compared to an age-matched control group we found that the IVF women were more prone to depressive and obsessive-compulsive symptoms as well as having increased scores for somatization.

Strengths and limitations

The major limitation in this study is that we do not have data on mental health and life events at the start of IVF treatment or during the 20 years that have passed for the participating women. We can assume that most of the women have experienced their share of difficulties related to one or more of major life events such as illness, job loss, death in the family and even trauma. However, it is reasonable to assume that the control group would be equally affected by such factors. Unfortunately, we have no information on educational level of the participants which might have influenced the results. Unfortunately, no additional information, for example parental status or fertility problems, was available for the reference group.

A great strength in this study is the high participation rate of 93%. The reason for this surprisingly high rate might be the that these women who were pioneers when IVF treatment was started in Sweden have a strong desire to be involved in studies concerning questions on health, IVF, and childlessness.

Interpretation

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These results are in line with those of previous studies which have found infertility treatment to be an emotionally draining process that can result in negative psychological consequences long term, especially for those whose treatment was unsuccessful, and for a long time remain a major life theme.[7, 9,20] Meanwhile, studies have also shown that long term psychological wellbeing is dependent on the ability to use coping skills [11,15-17] in order to overcome the grief process [18] and also on whether or not the woman still sustains a wish for biological children. [12] However, even if coping skills are successfully utilized, the grandparent phase, which the women of our study were just about to enter, might revoke the negative feelings that childlessness cause.[20] While some previous studies have shown that the difference in psychological symptoms depend on whether there are any children in the family, biological or adoptive,[9] others have shown only a positive influence of having biological children.[11] We found that some symptoms were decreased in both groups with children while the risk of depressive symptoms was only decreased in those with biological children.

Mental health is an important issue to study in the clinics where infertility investigations are conducted. The mental health and the lifestyle of women and men can be an indicator of, and explanation for, the fact that some women have trouble getting pregnant. For instance, anxiety disorders and depression might interfere with the couple's relationship and sexuality in a negative way thus decreasing quality of life. It is often believed that emotional stress before trying to achieve pregnancy, naturally or through infertility treatment will have a negative effect on pregnancy outcome. However, Boivin et al (2011) showed, in a meta-analysis on 14 prospective studies, that pretreatment emotional distress did not negatively influence treatment outcome [23]

In the future, we need to further explore the women who have a history of mental disorders or are vulnerable for mental ill health in the IVF setting in order to not jeopardize their future mental health which could be negatively affected if the infertility treatment is unsuccessful.

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Also, for women who show signs of suffering from a mental disorder at the time of infertility investigation, counseling and treatment are important and medically correct actions need to be taken before starting infertility treatment. Moreover, women who remain childless after infertility treatment might be in need of follow-up and counselling to cope with their situation many years after infertility treatment.

Conclusion

In conclusion, the majority of the women who have been treated with IVF 20-23 years previously appear to be in good mental health. However, women who remain childless after unsuccessful infertility treatment constitute a vulnerable group that needs to be observed in healthcare settings in order to prevent the evolvement of anxiety and depression symptoms and their side effects on somatic and psychological health.

Footnotes

Ethics**:** The study has been approved by the Human Research Ethics Committee, in Linköping University (nr 03-338, September 9th 2003).

Contributors: JV participated in analysis, manuscript drafting and critical discussion and final preparation of the manuscript. AJ participated in analysis, manuscript drafting and critical discussion. MB participated in study design, execution and analysis. GS was involved in the research idea, design and execution, analysis, manuscript drafting and critical discussion. GS is the guarantor for the study.

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Data sharing: Full dataset and statistical code available from the corresponding author at josefin.vikstrom@liu.se. Consent was not obtained but the presented data are anonymised and risk of identification is low.

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Table I. Demographic data for the women treated with IVF > 20 years ago (n=470)

		Total		No children		Biological children		Adoptive children		Biological and adoptive children		
		n	%	n	%	n	%	n	%	n	%	p-value
Employment status	Employed	349	74.3	66	78.6	189	78.8	75	87.2	19	79.2	0.369
	Missing	36	7.7	-	-	-	-	-	-	-	-	
Marital status	Married/ Cohabiting	411	87.4	55	58.5	240	93.0	91	100.0	25	100.0	<0.001
	Separated/divorced/ Other	57	12.1	39	41.5	18	7.0	0	0.0	0	0.0	
	Missing	2	.4	-	-	-	-	-	-	-	-	
Same partner	Yes	343	73.0	54	90.0	175	70.6	90	98.9	24	96.0	<0.001
	Missing	46	9.8									
Children	No Children	95	20.2	-	-	-	-	-	-	-	-	-
	Biological children	259	55.1	-	-	-	-	-	-	-	-	
	Adoptive children	91	19.4	-	-	-	-	-	-	-	-	
	Biological and adoptive children	25	5.3	-	-	-	-	-	-	-	-	
Age at follow-up	>=45 years old	289	61.5	75	78.9	136	52.5	63	69.2	15	60.0	<0.001

Significance level <.05

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Table II. The study-group women's self-perceived mental health assessed on the SCL-90

Somatization		Somatization %			Interpersonal Sensitivity%			Depression %			Anxiety %			Hostility %		
		No	Yes	p-value	No	Yes	p-value	No	Yes	p-value	No	Yes	p-value	No	Yes	p-value
Employment	Employed	80.4	80.0	0.962	81.2	69.0	0.108	81.8	65.8	0.017	81.8	59.3	0.004	80.5	78.6	0.860
Marital status	Married/cohabiting	88.4	76.2	0.095	88.4	80.0	0.176	88.8	76.9	0.030	88.6	75.9	0.042	88.1	80.0	0.347
	Separated/divorced/ Other	11.6	23.8		11.6	20.0		11.2	23.1		11.4	24.1		11.9	20.0	
Age at follow-up	>=45 years old	60.7	77.3	0.119	61.5	61.3	0.981	60.0	77.5	0.030	60.7	73.3	0.168	61.7	56.3	0.661
Same partner	Yes	81.1	75.0	0.541	81.5	70.8	0.197	81.2	77.4	0.609	81.3	73.9	0.381	81.3	66.7	0.203
Children	No children	19.9	27.3	0.159	19.4	32.3	0.188	18.4	40.0	0.009	19.5	30.0	0.420	20.0	25.0	0.961
	Biological children	56.0	36.4		56.0	41.9		56.7	37.5		55.9	43.3		55.3	50.0	
	Adoptive children	19.2	22.7		19.6	16.1		19.3	20.0		19.1	23.3		19.4	18.8	
	Biological and adoptive children	4.9	13.6		5.0	9.7		5.6	2.5		5.5	3.3		5.3	6.3	

Table II continued

		Phobic anxiety %			Paranoid Ideation %			Psychoticism %			Obsessive-Compulsive %		
		No	Yes	p-value	No	Yes	p-value	No	Yes	p-value	No	Yes	p-value
Employment	Employed	81.9	57.7	0.003	81.3	65.2	0.059	80.4	80.0	0.962	81.6	63.0	0.018
Marital status	Married/cohabiting	88.4	77.8	0.100	87.8	87.5	0.961	88.4	76.2	0.095	88.6	75.9	0.042
	Separated/divorced/ Other	11.9	22.2		12.2	12.5		11.6	23.8		11.4	24.1	
Age at follow-up	>=45 years old	60.2	82.1	0.021	61.9	54.2	0.449	60.7	77.3	0.119	60.7	77.3	0.119
Same partner	Yes	80.6	85.7	0.973	82.1	57.1	0.095	81.1	75.0	0.541	82.3	56.5	0.002
Children	No children	18.8	42.9	0.017	20.4	16.7	0.693	19.9	27.3	0.159	19.1	36.7	0.099
	Biological children	56.1	39.3		54.7	62.5		56.0	36.4		55.7	46.7	
	Adoptive children	19.9	10.7		19.7	12.5		19.2	22.7		20.0	10.0	
	Biological and adoptive children	5.2	7.1		5.2	8.3		4.9	13.6		5.2	6.7	

Significance level <.05

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Table III. The study group of 470 women compared to the reference group of 156 age matched women

	Cronbach's Alpha	IVF women n=463-470 Mean	Std. Deviation	Reference group age matched sample n=156 Mean	Std. Deviation	Effect size Cohen's Distance	p-value
Somatization	0.856	0.62	0.72	0.43	0.44	0.32*	<0.001
Obsessive-Compulsive	0.864	0.57	0.68	0.49	0.52	0.13	0.020
Interpersonal Sensitivity	0.884	0.41	0.68	0.42	0.47	0.02	0.763
Depression	0.921	0.62	0.80	0.52	0.58	0.14	0.017
Anxiety	0.870	0.49	0.70	0.43	0.48	0.10	0.079
Hostility	0.778	0.32	0.57	0.29	0.41	0.06	0.285
Phobic Anxiety	0.746	0.13	0.41	0.11	0.26	0.06	0.303
Paranoid Ideation	0.746	0.30	0.57	0.27	0.39	0.06	0.278
Psychoticism	0.762	0.15	0.41	0.14	0.24	0.03	0.599
Global Severity Index	0.975	0.41	0.60	0.38	0.38	0.06	0.291
Positive Symptom Distress Index	--	3.84	6.15	1.40	0.43	0.56**	<0.001
Positive Symptom Total	--	25.63	18.63	24.58	16.86	0.06	0.296

Significance level <.05
Effect size Cohen's Distance: ≥0.2small*, ≥0.5=medium**, ≥0.8=large***

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	Tables
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Mental health in women 20-23 years after IVF treatment: A Swedish cross-sectional study

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Mental health in women 20-23 years after IVF treatment: A Swedish cross-sectional study

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ABSTRACT

Objective: To assess self-perceived mental health in women treated with in vitro fertilization (IVF) 20-23 years previously, while comparing them to a reference group, and to determine any differences in mental health between those who had given birth, those who had adopted a child, those who had given birth and adopted a child and those who remained childless.

Design: A cross-sectional study.

Setting: A Center of Reproductive Medicine (RMC) at a Swedish University hospital.

Participants: 520 women who had undergone at least one IVF cycle at the University Hospital in Linköping between 1986 and 1989. 504 of the 520 women (97%) were eligible for follow-up. While 34 women declined, 93 percent (n=470) of the women agreed to participate. The reference group consisted of 150 women of the Swedish population included in a study that was used to validate the SCL-90.

Interventions: Follow-up was conducted in 2008-2009. The Symptom Check List – 90 (SCL-90) was used to measure the women's self-perceived mental health and a questionnaire specific for this study was used to retain demographic information.

Outcome measures: The SCL-90 assesses 9 primary dimensions; somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism. There is also a global index of distress.

Results: Women who had previously undergone IVF treatment were at increased risk of symptoms of depression (p=.017), obsessive compulsion (p=.02) and somatization (p=<.001) when compared to a reference group. In addition, the women who have remained childless are at increased risk of symptoms of depression (p=.009) and phobic anxiety (p=.017).

Conclusion: The majority of the women who have been treated with IVF 20-23 years previously appear to be in good mental health. However, women who remain childless and/or without partner after unsuccessful infertility treatment, constitute a vulnerable group even later on in life.

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Strengths and limitations of the study

- This is one of few studies on the long-term mental health of women who have been treated with IVF
- The follow-up period is exceptionally long at 20-23 years
- The participation rate was very high at ninety-three percent (n=470)
- Unfortunately, possible confounding factors such as educational level and life events could not be controlled for

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INTRODUCTION

Infertility, its investigations and treatment can cause psychological distress[1] , such as symptoms of anxiety and depression[2-4]. The infertility treatment itself further adds to the strain created by the infertility [5, 6]. In addition, childbirth is a known trigger for first time episodes of psychiatric illness [7-8]. However, Ross et al. (2011) found in their review that there were no significant differences in the risk of experiencing symptoms of depression between those who had conceived spontaneously and those who had been treated with IVF [9].

Studies using self-reported symptoms as outcome when examining psychological wellbeing up to ten years after IVF treatment have found that women who remain childless are at increased risk of anxiety,[6, 10] depression,[6,10, 11] and stress[11] and have a lower sense of coherence,[10] self-esteem [11] and satisfaction with life [11,12] than those who had given birth after treatment. Women who give birth as a result of treatment show a more positive long-term emotional status. [4]

Register-based studies using psychiatric diagnoses as outcome when examining risk of psychiatric illness after IVF treatment have varied in their results. Agerbo et al (2013) found no differences between those who had given birth or remained childless after treatment in regard to risk of psychiatric illness but that the risk was lower among those who had adopted children [13]. Another Danish register-based study by Baldur-Felskov et al. (2013) found that women who go through unsuccessful IVF treatment were at increased risk of hospitalization due to most psychiatric disorders but that the risk of affective disorders were lower than for those who had given birth as a result of treatment [14]. Meanwhile, Yli-Kuha et al. (2010)

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showed that the risk of depression was increased in those who had gone through an unsuccessful treatment [15].

In regard to long-term effects of infertility and its treatment, Gameiro et al. (2014) showed that women who had undergone infertility treatment 11-17 years previously suffered more mental health problems, when compared to the general population, and that a sustained child-wish negatively affected mental health.[16] Meanwhile, studies have shown that most women come to terms with their parenthood goals.[16-18] This shows that reorientation and coping after unsuccessful IVF treatment is important [4,19-21] and that couples may be in need of counselling after unsuccessful IVF treatment to resolve the grieving process.[22] Twenty years after infertility treatment the relationship quality in the couples who have previously undergone infertility treatment is good [23] although a qualitative study on 14 women showed that they still suffered negative effects of the infertility which were especially great when the women were going through the grandparent phase.[24] Most studies have shown that childlessness does not influence psychological well-being in elderly individuals.[25-27]

Thus, there are only a few studies on the mental health of women who have been treated with IVF from a long-term perspective. It is still unclear what effects infertility and its treatment has on women in a long-term perspective.

The aim of the present study was to assess self-perceived mental health in a group of women treated with IVF 20-23 years earlier. Secondly, we wanted to study possible differences in mental health between the four groups; those who had given birth, those who had adopted a child, those who had given birth and adopted a child and those who remained childless.

METHOD

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Subjects

All women (n=520) who had received at least one IVF treatment cycle at the Center of Reproductive Medicine, University Hospital in Linkoping between 1986 and 1989 were, in 2008 to 2009, sent an introductory letter asking them to participate in the study. Six of the women were deceased and ten women never received the letter, thus 504 out of 520 (97%) women were eligible for follow-up. Out of these, ten women returned the letter declining participation and 24 women did not answer. Thus, a total of 470 out of the 504 (93%) women eligible for follow-up agreed to participate. Out of the ninety-three percent (n=470) of the women who agreed to participate 55.1% (n=259) had biological children, 19.4% (n=91) had adoptive children, 5.3% (n=25) had both biological and adoptive children and 20.2% (n=95) had remained childless. As a reference group we used score mean values for 150 women of the general Swedish population. This data was derived from a population based study, through which the SCL-90 was validated, of women older than 40 years of age.[28, 29]

Treatment procedures 1986-1989

The couples were given three or more publically funded IVF treatments during this time period. Some of the couples might have had at least one child before entering treatment during this period. The upper age limit for the women was 38 years at the time of treatment. The waiting time from acceptance to treatment was approximately three years.

Outcome measures

The Symptom Check List – 90 (SCL-90) was used to measure the women's self-perceived mental health during the past week. The SCL-90 is an extensively used, multidimensional psychological status symptom inventory consisting of 90 items.[28,29] It is an objective method for symptom assessment requiring individuals to rate their psychopathological problems and symptoms. These symptoms are then used to compute scores for depression and

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anxiety. The scale is a five-point Likert scale ranging from "not at all" (0) to "extremely" (4). The SCL-90 assesses 9 primary dimensions; somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. The cut-off score for each primary dimension was set at the 95th percentile of self-reported symptoms in the study population in order to indicate a severe level of symptoms.[30,31] Hence > 95th percentile indicated "Yes" meaning the occurrence of clinically relevant symptoms and ≤95th percentile indicated "No". There is also a global index of distress that can be used as a summary dimension. The cut off score on the SCL-90 of < 70 was used as an indicator of mental health. [28]

Demographics

Age, employment status, marital status, same/different partner since time of IVF treatment, number of children (biological and adopted), number of miscarriages and number of IVF treatments were assessed through a questionnaire specific for this study. Those with same/different partner since time of IVF treatment thus constitute a subgroup to those who were married/cohabiting.

Statistics

Two sided Chi2-tests were used to analyze differences between the subgroups in regard to background variables and self-perceived mental health. Student's t-test, also two sided, was used to compare mean scores between all women who had received IVF treatment and those in the reference group. Effect sizes, using Cohen's distance was calculated in order to evaluate the magnitude of the differences of the mean scores between IVF treated women and women in the reference group. P-values <.05 was considered significant. All statistical analyses were performed using IBM SPSS version 19 (IBM Corporation, Armonk, NY).

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RESULTS

Demographics

The distribution of demographics across the three groups is shown in Table I. The majority of the women were older than 45 years at the time of follow-up. Those who had remained childless and those who had adopted children were significantly (p=<.001) more likely to be aged over 45 years than were those with biological children. While 41.5% (n=39) of the women without children were divorced or separated the corresponding number for the women with biological children were 7.0% (n=18) (p=<.001). Among those with adopted children, all women were married or cohabiting. Also, those with adopted children were the most likely to still be living with the same partner as they were at the time of IVF treatment (98.9%; n=90). Those without children (90%; n=54) who were cohabiting or married were more likely than those with biological children (70.6%; n=175) to have remained with the same partner (p=<.001) (Table I).

The women had on average been through 2.7 (range=1-10) IVF cycles and 189 of the women had experienced 1-10 miscarriages (mean=1.9).

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Table I. Demographic data for the women treated with IVF > 20 years ago (n=470)

		Total		No children		Biological children		Adoptive children		Biological and adoptive children		
		n	%	n	%	n	%	n	%	n	%	p-value
Employment status	Employed	349	74.3	66	78.6	189	78.8	75	87.2	19	79.2	0.369
	Missing	36	7.7	-	-	-	-	-	-	-	-	
Marital status	Married/ Cohabiting	411	87.4	55	58.5	240	93.0	91	100.0	25	100.0	<0.001
	Separated/divorced/ Other	57	12.1	39	41.5	18	7.0	0	0.0	0	0.0	
	Missing	2	.4	-	-	-	-	-	-	-	-	
Same partner	Yes	343	73.0	54	90.0	175	70.6	90	98.9	24	96.0	<0.001
	Missing	46	9.8									
Children	No Children	95	20.2	-	-	-	-	-	-	-	-	-
	Biological children	259	55.1	-	-	-	-	-	-	-	-	
	Adoptive children	91	19.4	-	-	-	-	-	-	-	-	
	Biological and adoptive children	25	5.3	-	-	-	-	-	-	-	-	
Age at follow-up	>=45 years old	289	61.5	75	78.9	136	52.5	63	69.2	15	60.0	<0.001

Significance level <.05

Self-perceived mental health

The women's own perceived mental health is displayed in table II. Women who had biological or adoptive children were less likely to experience symptoms of phobic anxiety than who had remained childless (p=.017) (Table II). Also, women who had biological children were also significantly less likely than women who had remained childless to experience symptoms of depression (p=.009). Women, who were separated, lived alone or who were unemployed showed more signs of depression, anxiety and obsessive-compulsive problems compared to women who were married and were gainfully employed. Women who were over 45 years of age also had more symptoms of mental illness. Women who had changed partner since the time of IVF had more obsessive-compulsive symptoms compared to

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women who still had the same partner but there were no other differences between these two groups (Table II).

Table II. The study-group women's self-perceived mental health assessed by the SCL-90

Sociodemographic factors in %*		Somatization			Interpersonal Sensitivity			Depression			Anxiety		
		No	Yes	p-value	No	Yes	p-value	No	Yes	p-value	No	Yes	p-v
Employment	Employed	80.4	80.0	0.962	81.2	69.0	0.108	81.8	65.8	0.017	81.8	5[illegible].3	0
Marital status	Married/cohabiting	88.4	76.2	0.095	88.4	80.0	0.176	88.8	76.9	0.030	88.6	7[illegible].9	0
	Separated/divorced/ Other	11.6	23.8		11.6	20.0		11.2	23.1		11.4	2[illegible].1	
Age at follow-up	>=45 years old	60.7	77.3	0.119	61.5	61.3	0.981	60.0	77.5	0.030	60.7	7[illegible].3	0
Same partner	Yes	81.1	75.0	0.541	81.5	70.8	0.197	81.2	77.4	0.609	81.3	[illegible].9	0
Children	No children	19.9	27.3	0.159	19.4	32.3	0.188	18.4	40.0	0.009	19.5	[illegible].0	0
	Biological children	56.0	36.4		56.0	41.9		56.7	37.5		55.9	4[illegible].3	
	Adoptive children	19.2	22.7		19.6	16.1		19.3	20.0		19.1	2[illegible].3	
	Biological and adoptive children	4.9	13.6		5.0	9.7		5.6	2.5		5.5	[illegible].3	

Table II continued

Sociodemograpic factors in %*		Phobic anxiety			Paranoid Ideation			Psychoticism			Obses
		No	Yes	p-value	No	Yes	p-value	No	Yes	p-value	N
Employment	Employed	81.9	57.7	0.003	81.3	65.2	0.059	80.4	80.0	0.962	8[illegible].6
Marital status	Married/cohabiting	88.4	77.8	0.100	87.8	87.5	0.961	88.4	76.2	0.095	[illegible].6
	Separated/divorced/ Other	11.9	22.2		12.2	12.5		11.6	23.8		[illegible].4
Age at follow-up	>=45 years old	60.2	82.1	0.021	61.9	54.2	0.449	60.7	77.3	0.119	[illegible].7
Same partner	Yes	80.6	85.7	0.973	82.1	57.1	0.095	81.1	75.0	0.541	[illegible].3
Children	No children	18.8	42.9	0.017	20.4	16.7	0.693	19.9	27.3	0.159	[illegible].1
	Biological children	56.1	39.3		54.7	62.5		56.0	36.4		[illegible].7
	Adoptive children	19.9	10.7		19.7	12.5		19.2	22.7		[illegible].0
	Biological and adoptive children	5.2	7.1		5.2	8.3		4.9	13.6		[illegible].2

*Percentage of individuals exhibiting the demographic factor for each category (Yes/ No).
P-values derived from Pearson chi square statistic with significance level <.05.
Cut-off for each primary dimension: Yes > 95th percentile (severe level of symptoms). No ≤95th percentile.

In regard to "Global severity index" and "Positive symptom total" the women who had experienced infertility within the couple and who had been through a number of IVF treatments 20-23 years earlier showed the same pattern as the reference group (Table III). Only on the "Positive symptom distress index" did the IVF group have a higher score indicating that these women had reported experiencing more intense symptoms. In regard to the specific symptoms, the women who had previously undergone IVF treatment were at increased risk of depressive and obsessive-compulsive symptoms as well as having increased scores for somatization (Table III).

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Table III. The study group of 470 women compared to the reference group of 156 age matched women

	Cronbach's Alpha	IVF women n=463-470 Mean	Std. Deviation	Reference group age matched sample n=156 Mean	Std. Deviation	Effect size Cohen's Distance	p-value
Somatization	0.856	0.62	0.72	0.43	0.44	0.32*	<0.001
Obsessive-Compulsive	0.864	0.57	0.68	0.49	0.52	0.13	0.020
Interpersonal Sensitivity	0.884	0.41	0.68	0.42	0.47	0.02	0.763
Depression	0.921	0.62	0.80	0.52	0.58	0.14	0.017
Anxiety	0.870	0.49	0.70	0.43	0.48	0.10	0.079
Hostility	0.778	0.32	0.57	0.29	0.41	0.06	0.285
Phobic Anxiety	0.746	0.13	0.41	0.11	0.26	0.06	0.303
Paranoid Ideation	0.746	0.30	0.57	0.27	0.39	0.06	0.278
Psychoticism	0.762	0.15	0.41	0.14	0.24	0.03	0.599
Global Severity Index	0.975	0.41	0.60	0.38	0.38	0.06	0.291
Positive Symptom Distress Index	--	3.84	6.15	1.40	0.43	0.56**	<0.001
Positive Symptom Total	--	25.63	18.63	24.58	16.86	0.06	0.296

Significance level <.05
Effect size Cohen's Distance: ≥0.2small*, ≥0.5=medium**, ≥0.8=large***

DISCUSSION

Principal findings

The majority of the women who had been treated with IVF 20-23 years previously reported few mental health problems. However, women who had remained childless 20 years after infertility treatment reported negative psychological consequences to a greater degree than those who had since become mothers. Childless women reported more symptoms of depression than were those with biological children and symptoms of phobic anxiety than were the women who had biological or adopted children. Women who had remained childless were to a greater degree separated or divorced, a group which to a greater degree reported

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suffering from depressive, anxiety and obsessive-compulsive symptoms. When all women who had undergone IVF treatment were compared to a reference group we found that the IVF women reported more depressive, obsessive-compulsive and somatization symptoms.

Strengths and limitations

The major limitation in this study is that we do not have data on mental health and life events at the start of IVF treatment or during the 20 years that have passed for the participating women. We can assume that most of the women have experienced their share of difficulties related to one or more of major life events such as illness, job loss, death in the family and even trauma but these are unfortunately not factors we could control for. However, it is reasonable to assume that the reference group would be equally affected by such factors. Unfortunately, we have no information on educational level of the participants which might have influenced the results. Also no additional information, for example parental status or fertility problems, was available for the reference group.

A great strength in this study is the high participation rate of 93%. The reason for this surprisingly high rate might be the that these women who were pioneers when IVF treatment was started in Sweden have a strong desire to be involved in studies concerning questions on health, IVF, and childlessness. Another strength is the long period of observation.

Interpretation

In accordance with previous studies the results of this study indicate that infertility treatment, especially when unsuccessful, might increase the risk of a negative psychological symptomatology.[10, 12,24] Meanwhile, studies have shown that long-term psychological wellbeing is dependent on the ability to use coping skills [14,19-21] in order to overcome the grief process [22] and also on whether or not the woman still sustains a wish for biological

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children. [16] However, even if coping skills are successfully utilized, the grandparent phase, which the women of our study were just about to enter, might revoke the negative feelings that childlessness cause.[24] While some previous studies have shown that the difference in psychological symptoms depend on whether there are any children in the family, biological or adoptive,[12] others have shown only a positive influence of having biological children.[14] Also, Munk-Olsen et al. found that adoptive parents were at reduced risk of psychiatric illness.[13] We found that some symptoms were decreased in both groups with children while the risk of depressive symptoms was only decreased in those with biological children.

Mental health is an important issue to study in the clinics where infertility investigations are conducted. The mental health and the lifestyle of women and men can be an indicator of, and explanation for, the fact that some women have trouble getting pregnant. For instance, anxiety disorders and depression might interfere with the couple's relationship and sexuality in a negative way thus decreasing quality of life. It is often believed that emotional stress before trying to achieve pregnancy, naturally or through infertility treatment will have a negative effect on pregnancy outcome. However, Boivin et al (2011) showed, in a meta-analysis on 14 prospective studies, that pretreatment emotional distress did not negatively influence treatment outcome [32]

Due to the limitations presented above, no firm conclusions regarding the long term consequences of infertility treatment on mental well-being can be drawn. However, our results indicate that women who remain childless after IVF treatment might be at risk of experiencing negative psychological symptoms 20 years after treatment. In the future, we need to further explore the women who have a history of mental disorders or are vulnerable for mental ill health in the IVF setting in order to not jeopardize their future mental health which could be negatively affected if the infertility treatment is unsuccessful. Also, for women who show signs of suffering from a mental disorder at the time of infertility

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investigation, counseling and treatment are important and medically correct actions need to be taken before starting infertility treatment. Moreover, women who remain childless after infertility treatment might be in need of follow-up and counselling to cope with their situation many years after infertility treatment.

Conclusion

In conclusion, the majority of the women who have been treated with IVF 20-23 years previously report few negative psychological symptoms. However, women who remain childless after unsuccessful infertility treatment constitute a vulnerable group that would likely benefit from being observed in healthcare settings in order to prevent the evolvement of anxiety and depression symptoms and their side effects on somatic and psychological health.

Footnotes

Ethics**:** The study has been approved by the Human Research Ethics Committee, in Linköping University (nr 03-338, September 9th 2003).

Contributors: JV participated in analysis, manuscript drafting and critical discussion and final preparation of the manuscript. AJ participated in analysis, manuscript drafting and critical discussion. MB participated in study design, execution and analysis. GS was involved in the research idea, design and execution, analysis, manuscript drafting and critical discussion. GS is the guarantor for the study.

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Data sharing: Full dataset and statistical code available from the corresponding author at josefin.vikstrom@liu.se. Consent was not obtained but the presented data are anonymised and risk of identification is low.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	Tables
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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