Female infertility, infertility-associated diagnoses, and comorbidities: a review

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Abstract

Purpose The purpose of the study is to evaluate existing literature for possible associations between female infertility, infertility-associated diagnoses, and the following areas of disease: psychiatric disorders, breast cancer, ovarian cancer, endometrial cancer, cardiovascular disease, and metabolic dysfunction.

Methods The design of the study is a literature review. The patients were women included in 26 selected studies due to a diagnosis of infertility or a reproductive disorder associated with infertility. This study has no interventions, and the main outcome measure is the association between female infertility or a related diagnosis and psychiatric disorders, breast cancer,

ovarian cancer, endometrial cancer, cardiovascular disease, and metabolic dysfunction.

Results Female infertility and related reproductive disorders may have ramifications for women beyond reproductive health. An analysis of publications shows that women with infertility had higher rates of psychiatric disorders and endometrial cancer than the general population [1–10]. Data is conflicting about whether infertile women are at increased risk for breast cancer and ovarian cancer [7, 8, 10–20]. A generalized diagnosis of infertility was not clearly associated with an increased risk of cardiovascular disease or metabolic dysfunction, but women with infertility related to polycystic ovarian syndrome (PCOS) do appear more likely to develop cardio-

Capsule There is a growing body of literature addressing the impact of female infertility on long-term health. This review evaluates 26 studies, investigating possible correlations between infertility and psychiatric illness, breast cancer, ovarian cancer, endometrial cancer, cardiovascular disease, and metabolic dysfunction. Overall, higher rates of psychiatric illness and endometrial cancer were seen in infertile women. It is unclear whether infertility results in increased rates of breast cancer and ovarian cancer, and data are conflicting regarding correlations between generalized infertility and cardiovascular disease and metabolic dysfunction. This study summarizes current literature and can guide practitioners in counseling infertile patients.

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vascular disease and metabolic disorders such as diabetes than the general population [16, 21–26].

Conclusions Female infertility and associated diagnoses have overall health implications. Beyond treatment of patients' immediate reproductive needs, healthcare professionals must be aware of the broader health impact of specific causes of infertility in order to provide accurate counseling regarding long-term risk.

Keywords Infertility · In vitro fertilization · Malignancy · Somatic health · Fertility drugs

Introduction

Infertility is common, with recent publications quoting a 9 to 18% prevalence in the general population [27]. In 2008, 61,430 neonates were born as the result of assisted reproductive technology (ART) [28]. According to the National Summary Report from the Society for Assisted Reproductive Technology, there were 190,394 cycles initiated in 2014 for egg retrieval, frozen embryo transfer, and frozen egg thawing [29]. These statistics highlight the impressive numbers of women undergoing fertility treatment. Since the late 1970s when ART became available, clinical focus has been placed on meeting the immediate reproductive needs of patients with infertility. Much has been studied about the impact of infertility and ART related to pregnancy and neonatal health. Increased risks of preterm delivery, low birthweight, and perinatal mortality are well documented [30]. However, much less is known about the associated comorbidities of infertility for women with this diagnosis or with diagnoses such as PCOS and endometriosis, which are known to contribute to infertility. It is likely that multiple factors play a role in the infertile woman's predisposition to develop subsequent somatic health issues. Underlying genetic abnormalities, hormonal imbalances related to chronic anovulation or elevated androgens, or environmental factors may at least partially explain recognized associations between infertility and specific disease processes. However, until recently, tracking the long-term health outcomes in infertile women was not commonplace.

There is a growing body of data to support the idea that infertility has implications that go beyond the immediate reproductive needs of patients. Approximately 5–10% of infertile women may have underlying genetic abnormalities such as chromosome aberrations, single or multiple gene mutations, and polymorphisms. A significant portion of infertility may at least partially be explained by exposure to environmental factors, endocrine disruptions, and hormonal imbalances [31]. A possible increased risk of gynecologic malignancies in infertile women has been proposed in multiple studies [10, 32–36]. Furthermore, endometriosis has been related to higher rates of melanoma, asthma, autoimmune

disease, atopic disease, cardiovascular disease, and ovarian cancer [16]. PCOS has been linked with increased waist circumference, insulin resistance, elevated serum insulin levels, higher lipoprotein ratios, type II diabetes, hyperlipidemia, and increases in central/visceral adiposity even in the setting of normal BMI [6, 22].

To date, there are very few comprehensive reviews of infertility comorbidities. We undertook a literature review to examine current data linking infertility and infertility-associated reproductive disorders to long-term health consequences in women. While the underlying cause of infertility in women varies, our hypothesis is that female infertility and disorders such as PCOS and endometriosis are markers for future health problems. Genetic, epigenetic, and environmental exposures may predispose infertile women to future disease states. If clear associations between infertility and comorbidities are identified, emphasis can be placed on targeting at-risk women for further testing or counseling.

Materials and methods

A review of the literature relevant to infertility and its impact on overall female health was conducted. An unrestrained PubMed/MEDLINE search was performed in July 2016, which yielded 425 studies. The search used the following MeSH terms in combination with female infertility: ovarian neoplasms, cancer risk, drugs and infertility, ovarian tumors, fertility agents, breast neoplasms, breast cancer, fertility therapy, fertility treatment, polycystic ovarian syndrome, non-alcoholic fatty liver disease, endometriosis, major chronic diseases, thyroid diseases, thyroid disorders, thyroid gland, lipoproteins, insulin resistance, coronary disease, coronary heart disease, BRCA1, BRCA2, germline mutations, anti-mullerian hormone, ovarian insufficiency, endometrial neoplasms, endometrial cancer, fertility drugs, mental disorders, anxiety, depression, and distress.

These search terms were selected based on the previously determined areas of interest, which included female infertility's connection to psychiatric disorders, breast cancer, ovarian cancer, endometrial cancer, metabolic dysfunction, and cardiovascular disease. The University of Utah Health Sciences Library staff assisted in the literature search to ensure that duplicate results were eliminated and that the search terms included as many relevant studies as possible.

Of the 425 initial results, 415 were primarily in English or had been translated to English. The titles of the articles were reviewed individually for relevance to the topic. Ultimately, of the articles reviewed, 26 were chosen by the study authors to be highly relevant. The 26 articles were reviewed in their entirety and are included in the study below. Of note, female infertility was a primary inclusion criterion for many of the studies reviewed. Studies which included populations of associated reproductive disorders such as PCOS and

Table 1 Characteristics of studies linking infertility to mental health

Study	Location	Study type	Year	Cases (n)	Study-specific infertility definition	Findings in female subjects
Valoriani et al. [1]	Italy	Cross-sectional	2016	309 couples	Initial visit with fertility specialist	Increased psychosocial distress Increased depression
Veltman-Verhulst et al. [2]	UK	Meta-analysis	2016	2384	Diagnosis of PCOS	Increased depression Increased anxiety Increased emotional distress
Gokhan et al. [3]	Turkey	Case-control	2013	86	Diagnosis of PCOS	Increased depression Increased anxiety
Jedel et al. [4]	Sweden	Case-control	2009	30	Diagnosis of PCOS	Increased anxiety No difference in depression
Baldur-Felskov et al. [5]	Denmark	Retrospective cohort	2013	98,320	Evaluation for fertility problems 1973–2008	Increased hospitalization for alcohol abuse, drug abuse, and schizophrenia No difference in OCD No difference in anxiety No difference in eating disorders
Hart & Doherty [6]	Australia	Retrospective cohort	2015	2566	Diagnosis of PCOS	Increased stress/anxiety Increased depression Increased drug-related hospitalizations Increased self-harm

endometriosis were also included given the inherent link between these diagnoses and infertility.

Results

Infertility and mental health

Six studies included in this review evaluated the impact of infertility on mental health. See key findings in Table 1. Universally, authors concluded that women with a history of infertility or an infertility-related diagnosis, specifically PCOS, were at increased risk to develop mental health disorders [1–6]. Four out of the six studies that found correlations with mental health issues used women with PCOS as their primary population [2–4, 6]. Depression risk was found to be elevated in four out of the six studies based on scores from validated scales such as the Edinburgh Depression Scale [1–3, 6]. Five of the six studies noted significant increases in diagnoses of anxiety or psychosocial distress in the specific study populations [1–4, 6].

The sole study which did not find an increase in anxiety was by Baldur-Felskov et al. This study was a retrospective cohort study published in 2013 that included 98,320 Danish women who were evaluated for infertility between 1973 and 2008, with a median follow up of 11.3 years. Women who sought infertility treatment were tracked through medical registries to determine rates of subsequent psychiatric hospitalizations. While there was

no statistically significant increase in hospitalizations related to anxiety in the PCOS/infertile population, it is difficult to assess whether actual levels of anxiety were elevated but simply did not lead to subsequent hospitalizations. A main drawback of the Baldur-Felskov study was the fact that only inpatient hospitalizations were tracked, likely underestimating the true correlation between infertility and psychiatric disease. Importantly, the Baldur-Felskov study did note a significant increase in hospitalizations related to alcohol and drug abuse in the PCOS/infertile population [5].

While causation cannot be confirmed in any of these studies, it is important to note that a correlation exists between infertility/PCOS and mental health disorders, with some presentations near the time of the infertility diagnosis and others years later. An awareness of this correlation can help clinicians understand the unique challenges faced by women with infertility. Whether a specific biologic or environmental link between infertility and mental health exists remains unclear.

Infertility and gynecologic malignancy

The connection between female infertility and gynecologic malignancy is one of the most studied aspects of the impact of infertility on somatic health. Specifically, studies have evaluated whether infertility is correlated with breast cancer, ovarian cancer, and endometrial cancer. These gynecologic malignancies will be discussed individually, with relevant studies included in table format.

Table 2 Characteristics of studies linking infertility to breast cancer

Study	Location	Study type	Year	Cases (n)	Study-specific population	Findings in female subjects
Venn et al. (1995) [10]	Australia	Retrospective cohort	1995	10,358	Women undergoing IVF Stimulated IVF (n = 5564) Natural IVF (n = 4794)	No significant difference in breast cancer rates compared to general population Stim IVF: SIR 0.89 (95% CI 0.55–1.46) Nat IVF: SIR 0.98 (95% CI 0.62–1.56) Infertile women had 1.53 cm ³ higher absolute dense volume of breasts (95% CI 0.7–2.35) Only women who had previously received ovarian stimulation had higher absolute dense volume Unclear whether breast density correlates to breast cancer
Lundberg et al. [11]	Sweden	Cross-sectional	2015	8963	Patient self-reported history of infertility	OR for PCOS was higher for premenopausal breast CA (2.74, 95% CI 1.13–6.63) but not postmenopausal breast CA (0.87, 95% CI 0.44–1.71). PCOS may play a role in the diagnosis of premenopausal breast CA.
Kim et al. [12]	S Korea, USA	Case-control	2016	1508 cases 1556 controls	1508 women w/newly diagnosed breast CA 67 of these women (2.2%) had diagnosed PCOS or infertility	Infertility does not appear to be a risk factor for breast cancer. Results are contradictory. 3 studies showed increased breast cancer risk in infertile women; 7 did not. Risk of breast CA in women w/PCOS was not significantly increased (OR 0.95, 95% CI 0.64–1.39) Breast cancer incidence was no greater than expected in either IVF group Stimulated: SIR 0.91 (95% CI 0.74–1.13) Natural: SIR 0.95 (95% CI 0.73–1.23) Women exposed to ART had an elevated risk of breast CA (HR 1.20, 95% CI 1.01–1.42) 3 studies with significant positive associations between breast CA and endometriosis. 4 studies w/modest positive association between endometriosis and breast CA (not significant). 4 studies showed no clear association. 4 studies reported decrease risk of breast CA in patients with endometriosis.
Gabriele et al. [13]	France	Systematic review Meta-analysis	2016	10 publications	Infertile women. Definition varied by study	Women treated with ART had a lower risk of breast CA as well as lower risk for all CA (SIR 0.78; 95% CI 0.73–0.83)
Barry et al. [8]	UK	Systematic review Meta-analysis	2014	11 studies (919 women with PCOS) 29,700	Diagnosis of PCOS	
Venn et al. (1999) [7]	Australia	Retrospective cohort	1999	8037	Women undergoing IVF Stimulated IVF (n = 20,656) Natural IVF (n = 9044)	
Reigstad et al. [14]	Norway	Retrospective cohort	2015	15 publications	8037 women w/breast cancer. 138 (1.7%) had previous ART Women with endometriosis	
Kvaskoff et al. [16]	USA, France, Sweden	Meta-analysis	2015			
Luke et al. [17]	USA	Longitudinal cohort	2015	113,226	Women treated with ART 2004–2009	

SIR standardized incidence ratio

Breast cancer

In this review, nine studies evaluated potential links between a diagnosis of infertility or the use of fertility drugs on the subsequent development of breast cancer. Overall, results were conflicting. Refer to Table 2 for study details. Seven studies showed no significant difference or contradictory evidence between women with infertility and subsequent breast cancer diagnoses [7, 8, 10–13, 16]. One study by Luke et al. showed a lower risk of breast cancer in women with infertility. This study evaluated 113,226 women in the United States who received assisted reproductive technology (ART). Data from state cancer registries showed that women who received ART had a statistically significant decrease in subsequent breast cancer diagnoses [17]. One study showed a positive correlation between a diagnosis of infertility and the development of breast cancer [14].

While not included in Table 2, publications have discussed a possible link between infertility and the BRCA-1 mutation, which is a well-documented risk factor for the development of breast cancer. Oktay, Phillips, and Wang showed in three separate studies that BRCA-1 mutations were associated with low anti-mullerian hormone (AMH) levels and low ovarian response rates [37–39]. This subset of women, as expected, is at higher risk to develop breast cancer in the future. These studies were not included in the review itself because at this point, it may be premature to state that BRCA-1 mutations are an independent predictor of infertility. While the studies by Oktay, Phillips, and Wang showed low AMH and low ovarian response rates in women with BRCA-1 mutations, this information is more predictive of poor response to ART than true infertility. Data is currently lacking whether BRCA-1 mutations are an independent predictor of infertility. The study by Reigstad et al. which documented an increased risk of breast cancer in infertile patients evaluated women who had received ART. This study showed a link between women who received ART and higher future breast cancer rates [14]. One key factor that may be confounding all of these studies is the demonstrated increase in breast cancer risk among nulliparous women, as infertile women are more likely to remain nulliparous [40].

Ovarian cancer

A link between ovarian cancer and infertility has also yielded conflicting results. Of the 26 studies in this review, nine evaluated correlations between infertility and ovarian cancer. Please refer to Table 3 for study details. Only one of the nine studies relating to ovarian cancer showed a clear increase in ovarian cancer risk for women with an infertility-associated diagnosis. This study by Cirillo et al. published in 2016 showed a positive link between irregular menses and subsequent risk of developing ovarian cancer [18]. While Cirillo's study looked at irregular menses rather than a specific

diagnosis of infertility, many women with infertility caused by PCOS have irregular menstrual cycles, which makes this finding noteworthy. However, it must be noted that Cirillo's study included women who had previously given birth, indicating that despite a history of irregular menses, the women in the study may not have been infertile.

The remaining eight studies showed conflicting data about whether women with infertility were at a higher risk to develop ovarian cancer. Specific subgroups of women did appear to be at higher risk for subsequent ovarian cancer. These subgroups included women with unexplained infertility, parous women with only one delivery as opposed to multiple deliveries following reproductive technology, women with PCOS, and women who had used progesterone therapy as part of their fertility treatment [8, 10, 15, 19]. In a meta-analysis of 21 studies by Kvaskoff et al., 20 studies showed an elevated ovarian cancer risk in women with endometriosis, while one study failed to show this association [16]. Evaluating women with a general diagnosis of infertility appears to yield conflicting results, but certain subgroups of infertile women may benefit from additional testing or counseling related to the topic of ovarian cancer. It is also important to note that the studies above were inconsistent in controlling for nulliparity, which is a known risk factor for ovarian cancer.

Endometrial cancer

Five of the 26 studies included in this review evaluated possible links between infertility and endometrial cancer. See Table 4 for study details. Four of the five studies related to endometrial cancer showed at least certain subgroups of the study population with a statistically significant elevation in cancer risk [7–10]. Women with unexplained infertility or women diagnosed with PCOS at a young age showed substantial elevations in endometrial cancer risk [8, 10]. Two of the five studies evaluated specific reproductive therapy techniques as they related to endometrial cancer. Endometrial cancer risk was found to be elevated in women receiving natural cycle IVF as well as women who began using Clomid therapy at less than 30 years of age [7, 9].

The only study which did not find an increase in endometrial cancer risk in infertile women was a longitudinal cohort study published in 2015 by Luke et al. which showed a decrease in risk of endometrial cancer in infertile women who received ART when compared to infertile women who did not receive ART, although this decreased risk was not statistically significant [17]. Overall, infertility related to PCOS seems to show a strong relationship with subsequent endometrial cancer risk. Many of the statistical risks published were significantly elevated, which makes this area of study highly relevant for clinical practice. PCOS is intrinsically linked to infertility, but whether the primary cause of endometrial cancer in these

Table 3 Characteristics of studies linking infertility to ovarian cancer

Study	Location	Study type	Year	Cases (n)	Study-specific population	Findings in female subjects
Venn et al. (1995) [10]	Australia	Retrospective cohort	1995	10,358	Women undergoing IVF Stimulated IVF (n = 5564) Natural IVF (n = 4794)	No significant difference in ovarian cancer rates compared to general population Stim IVF: SIR 1.70 (95% CI 0.55–5.27) Nat IVF: SIR 1.62 (95% CI 0.52–5.02) Women w/unexplained infertility had higher ovarian CA risk: RR 19.19 (95% CI 2.23–165) No significant elevation in overall ovarian CA risk: HR 1.56 (95% CI 0.94–2.60) Women w/1 delivery: HR for ovarian CA slightly elevated (HR 2.00, 95% CI 1.08–3.65) Women w/irregular menses had a 2-fold increased risk of ovarian CA in incidence and mortality by age 70 over 50-year follow up. 95% CI 1.1–3.4
Reigstad et al. [15]	Norway	Retrospective cohort	2015	16,525	Women who gave birth after undergoing ART	
Cirillo et al. [18]	USA	Prospective cohort	2016	15,528 mothers 116 (0.75%) w/ovarian CA	Irregular menses by self report and medical record in women with and without ovarian CA	Risk of ovarian CA in women w/PCOS was not significantly increased (OR 1.41, 95% CI 0.93–2.15) In studies w/younger women (<54 yo), ovarian CA risk was elevated for PCOS women (OR 2.52, 95% CI 1.08–5.89) Ovarian cancer incidence was no greater than expected in either IVF group Stimulated: SIR 0.88 (95% CI 0.42–1.84) Natural: SIR 1.16 (95% CI 0.52–2.59) 20 studies reported positive associations between endometriosis and ovarian CA.
Barry et al. [8]	UK	Systematic review Meta-analysis	2014	11 studies (919 women with PCOS)	Diagnosis of PCOS	1 study showed no association. Women treated with ART had a non-statistically significant higher risk of ovarian CA. Essentially no difference. (SIR 0.96–1.18) Overall risk of borderline ovarian tumors not associated w/fertility drugs (RR 1.0, 95% CI 0.67–1.51) Use of progesterone increased risk of borderline serous ovarian tumors (RR 1.82, 95% CI 1.03–3.24) 7 cohort studies showed no elevation in risk of invasive ovarian CA. 7 case-control studies showed no increased risk of invasive ovarian CA. 2 cohort studies showed increased risk of invasive ovarian CA. 2 case-control studies showed 2–3 fold increase in borderline ovarian CA risk Overall, no increased risk of invasive ovarian CA; possible increased borderline tumor risk
Venn et al. (1999) [7]	Australia	Retrospective cohort	1999	29,700	Women undergoing IVF Stimulated IVF (n = 20,656) Natural IVF (n = 9044)	
Kvaskoff et al. [16]	USA, France, Sweden	Meta-analysis	2015	21 publications	Women with endometriosis	
Luke et al. [17]	USA	Longitudinal cohort	2015	113,226	Women treated with ART 2004–2009	
Bjornholt et al. [19]	Denmark	Retrospective case-cohort	2015	96,545	Danish women who had been treated in fertility clinics 1963–2006	
Rizzuto et al. [20]	UK	Systematic review	2013	11 case-control 14 cohort n = 182,972	Women with exposure to ovarian stimulating drugs for treatment of infertility. Borderline or invasive ovarian CA	

SIR standardized incidence ratio

Table 4 Characteristics of studies linking infertility to endometrial cancer

Study	Location	Study type	Year	Cases (<i>n</i>)	Study-specific population	Findings in female subjects
Venn et al. (1995) [10]	Australia	Retrospective cohort	1995	10,358	Women undergoing IVF Stimulated IVF (<i>n</i> = 5564) Natural IVF (<i>n</i> = 4794)	Increased overall risk of endometrial cancer compared to general population All 10,358 pt: SIR 2.84 (95% CI 1.18–6.81) Women w/unexplained infertility had higher endometrial CA risk: RR 6.34 (95% CI 1.06–38)
Barry et al. [8]	UK	Systematic review Meta-analysis	2014	11 studies (919 women with PCOS)	Diagnosis of PCOS	Risk for endometrial CA in women w/PCOS was significantly increased (OR 2.79, 95% CI 1.31–5.95) In studies w/younger women (<54 yo) endometrial CA risk was elevated further (OR 4.05, 95% CI 2.42–6.76)
Venn et al. (1999) [7]	Australia	Retrospective cohort	1999	29,700	Women undergoing IVF Stimulated IVF (<i>n</i> = 20,656) Natural IVF (<i>n</i> = 9044)	Endometrial cancer incidence was no greater than expected in stimulated IVF group but was elevated in natural IVF group: Stimulated: SIR 1.09 (95% CI 0.45–2.61) Natural: SIR 2.47 (95% CI 1.18–5.18) Women w/unexplained infertility had significantly higher endometrial CA rates: Unexplained: SIR 4.59 (95% CI 1.91–11.0)
Luke et al. [17]	USA	Longitudinal cohort	2015	113,226	Women treated with ART 2004–2009	Women treated with ART had a non-statistically significant decrease in risk of endometrial CA. (SIR 0.73–0.82)
Brinton et al. [9]	USA	Retrospective cohort	2013	9832	Women seen for infertility 1965–1988	No statistically significant increase in endometrial CA risk in women who used Clomid: HR 1.39 (95% CI 0.96–2.01) or gonadotropins: HR 1.34 (95% CI 0.76–2.37). Increased risk of endometrial CA if women began Clomid at <30 yo (HR 1.93, 95% CI 1.24–3.00)

SIR standardized incidence ratio

Table 5 Characteristics of studies linking infertility to metabolic dysfunction and cardiovascular disease

Study	Location	Study type	Year	Cases (n)	Study-specific population	Findings in female subjects
Parikh et al. [21]	USA	Observational	2016	72,982	Postmenopausal women in the Women's Health Initiative	Reproductive risk factors associated with post-menopausal coronary heart disease include: young age at 1st birth, number of stillbirths, number of miscarriages, lack of breastfeeding (C-statistic: 0.675) Menstrual irregularity was linked to PCOS, which is correlated to cardiovascular risk factors. When corrected for HTN, HLD, DM, irregular menses alone is not a risk factor for CHD Lipoprotein ratios (TG/HDL) are directly correlated to insulin resistance in PCOS. Infertility related to PCOS is correlated with increased waist circumference, insulin resistance (IR), and higher lipoprotein ratios (TG/HDL-C) compared to healthy controls. TG/HDL-C ratio had sensitivity 63.6%, specificity 84.4% as marker of IR. Infertility related to PCOS increases central adiposity even if overall BMI is normal. Infertility is 10 times more common in women with PCOS. Up to 50% of women with PCOS have infertility in some studies.
Ghaffarzad et al. [22]	Iran	Case-control	2016	36 infertile women, 29 controls	Infertile women w/PCOS	In the US, up to 80% of women with PCOS are obese. 85% of women with PCOS have hyperinsulinemia. 20% of PCOS women develop type 2 DM MI rates 7× higher in PCOS women BMI, Ferriman Gallwey scores, insulin level, DHEAS, testosterone, LH, thyroid volume, and IGFBP-3 levels higher in PCOS patients Increased thyroid volume in women with PCOS appears to be related to luteinizing hormone (LH). Prevalence of metabolic syndrome (MetS) in PCOS 28.8% PCOS increases risk for MetS Of the 215 patients w/PCOS, waist circumference >88 cm in 78.6%, HTN present in 9.3%, FBS >110 in 6%, TG >150 in 47%, HDL <50 in 86% 4 studies reported positive associations between endometriosis and increased cardiovascular risk Prevalence of non-alcoholic fatty liver disease was significantly higher in PCOS patients. Overall OR 3.93 (CI 2.17–7.11) Increased hospital admissions for diabetes (12.5 vs 3.8%), obesity (16.0 vs 3.7%), hypertensive disorder (3.8 vs 0.7%), ischemic heart disease (0.8 vs 0.2%), cerebrovascular disease (0.6 vs 0.2%), arterial and venous disease (0.5 vs 0.2%) and 10.4 vs 5.6%)
El Hayek et al. [23]	Lebanon	Literature analysis	2016	195 articles	Women with PCOS	
Polat et al. [24]	Turkey	Case-control	2016	70 PCOS patients, 84 controls	Women with PCOS	
Zahiri et al. [25]	Iran	Cross sectional	2016	215 PCOS women: 62 with metabolic syndrome, 153 without	Women with PCOS	
Kvaskoff et al. [16]	USA, France, Sweden	Meta-analysis	2015	21 publications	Women with endometriosis	
Ramezani-Binabaj et al. [26]	Iran	Meta-analysis	2014	7 studies	Women with PCOS	
Hart et al. [6]	Australia	Retrospective cohort	2015	2566	Women with PCOS	

women stems from PCOS, obesity, their infertility diagnosis, or a combination of these factors remains unclear.

Metabolic dysfunction and cardiovascular disease

While gynecologic malignancies have been the main focus of research related to the long-term impact of infertility, several studies have evaluated other disease processes. Eight of the 26 studies in this review evaluated the impact of infertility on metabolic dysfunction or cardiovascular health. See Table 5 for study details.

The eight studies detailed in Table 5 show correlations between infertility and increased cardiovascular risk, higher myocardial infarction rates, higher insulin resistance, increased waist circumference, higher rates of central adiposity, increased diagnosis of metabolic syndrome, and increased risk of non-alcoholic fatty liver disease [16, 21–26]. These studies also show increased hospitalizations for various disease processes in women with a known history of PCOS [6]. It is important to note that of the eight studies detailing elevations in somatic health risks, six of these studies specifically included a population of women with PCOS [22–26].

PCOS seems to play a prominent role in the development of overall health problems, likely due to its intrinsic relationship to metabolic syndrome. Endometriosis also seems to elevate an individual's cardiovascular risk [16]. Findings of the above studies show that counseling and awareness of overall metabolic health risks are necessary when dealing with the PCOS and endometriosis populations.

Discussion

There is a rapidly growing body of knowledge that demonstrates that women with infertility or infertility-associated diagnoses may be predisposed to develop other health problems that may not present simultaneously with their infertility. While we cannot definitively state that infertility causes health problems such as psychiatric disorders, gynecologic malignancies, or other somatic problems, the studies included in this review show that infertility is not an isolated diagnosis, but rather part of a complex interplay of risk factors that may have an overall health impact for women.

Strong correlations exist between infertility and mental health disorders. Rates of depression were elevated in four out of the six studies included in this review, while five of the six studies noted significant increases in diagnoses of anxiety or psychosocial distress in women with an infertility diagnosis. Many studies evaluating mental health are limited by the fact that psychiatric disorders may be underdiagnosed or treated in an outpatient setting and therefore excluded from evaluation when hospital admissions are used as inclusion criteria [5]. Based on the studies included, a majority of

patients with subsequent mental health challenges appear to have a diagnosis of PCOS [1–4, 6]. The relationship between PCOS and mental health is not yet clear but may be independent of a strict diagnosis of infertility. Ongoing research has suggested that testosterone levels may play a role in brain development, which could provide a possible explanation for this association [41]. Health care providers who care for women with infertility or PCOS should be aware that their patients may face challenges either at time of consultation for infertility or in the future related to anxiety, depression, and substance abuse. A thorough assessment of the psychiatric needs of infertility patients is crucial to providing comprehensive care to this unique patient population.

No strong correlations can be made relating infertility to breast and ovarian cancer. Patients with BRCA-1 mutations have well-documented lower AMH levels and low ovarian response rates to ART, but no convincing evidence exists to date to show that these women have decreased natural fertility [37–39]. It is important to note that the studies which discussed BRCA-1 mutations did not show correlations between low AMH and poor ovarian response in women with BRCA-2 mutations. Further studies are necessary to elucidate whether specific subsets of infertile women may truly be at risk to develop these malignancies in the future. Nulliparity and its relationship to infertility remains a significant confounder in many of the studies which have been published. Controlling for nulliparity is imperative when evaluating a possible link between infertility and breast or ovarian cancer [7, 8, 10, 11, 13, 15–17, 19, 20].

The health implications of PCOS have been thoroughly documented, including an increased risk for endometrial cancer, metabolic disorders, cardiovascular disease, obesity, and a predisposition to insulin resistance or outright diabetes [16, 21–26]. Since PCOS makes women 10 times more likely to develop infertility, it is crucial to understand the connections between a diagnosis of PCOS and overall health [23]. The nature of PCOS makes the study of this disease process challenging. There is significant overlap between PCOS, infertility, and the risk factors for poor overall health that often accompany this diagnosis. Appropriate patient counseling and attempts to encourage healthy lifestyle in women with PCOS may help mitigate some of the health risks associated with PCOS, but significant confounders remain in studies which evaluate the role of PCOS, infertility, and health outcomes.

Given the heterogeneity observed in the findings of the studies discussed, attempts to correlate infertility to various aspects of female health are rarely straightforward. By continuing to evaluate specific subsets of women with infertility, future studies may be able to better delineate which causes of infertility are associated with specific somatic outcomes. It is encouraging to see that over the past few years, studies have highlighted the impact of infertility on non-reproductive health outcomes.

Limitations

As with any literature review, the methodologic quality of the included studies was variable. Some of the studies included relatively small sample sizes. Some of the studies evaluated specific ethnic populations which may lack external validity. It is also very possible that not all relevant studies were included. This review included only studies published in English, possibly excluding other valuable studies. Publication bias and selection bias could also influence findings. One of the major pitfalls of this review is that a specific cause of infertility was often not well-clarified in the individual studies. While certain studies did look specifically at endometriosis or PCOS, which are correlated with infertility, several studies included patients based on an unspecified diagnosis of infertility. Different causes of infertility may be associated with different health risks, which may not have been clearly shown.

Implications

This systematic review suggests that women with infertility may be at higher risk to develop health issues outside of their immediate infertility. The review demonstrates the need to provide truly comprehensive care to women with a diagnosis of infertility, which may include a referral to a medical clinic following infertility treatment. Additional screening tests, lifestyle modifications, and treatment appear warranted in women with PCOS. Overall, infertility is a complex healthcare issue, but clarifying an exact diagnosis for a patient's infertility when possible may help to risk stratify patients to direct counseling regarding the impact on somatic health.

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