Psychological, perinatal, lifestyle and health-economic aspects of the polycystic ovary syndrome

What really matters for the patient, her family and the society

The picture on the cover is drawn by my best friend, Griet Huysentruyt.

The polycystic ovary syndrome is often compared with a chameleon; an animal that changes color according to different circumstances. Similarly, the “color” of the polycystic ovary syndrome differs from person to person and changes over time. The tail of the chameleon on the picture symbolizes the polycystic ovarian morphology.

This dissertation received an educational grant from Merck Serono from November 2006 till October 2008, and was financially supported for operating costs by the Artevelde University College Ghent from January 2007 till December 2008. The author of this dissertation was holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research from September 2013 till August 2014.

University Press, Leegstraat 15, 9060 Zelzate, Belgium

info@universitypress.be – www.universitypress.be

Psychological, perinatal, lifestyle and health-economic aspects of the polycystic ovary syndrome

What really matters for the patient, her family and the society

Dissertation submitted by Veerle De Frène to obtain the degree of “Doctor in Medical Sciences” at the Ghent University

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List of abbreviations

AMH	Antimüllerian hormone
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
BSRM	Belgian Society for Reproductive Medicine
CBT	Cognitive-behavioral therapy
CC	Clomiphene citrate
CEA	Cost-effectiveness analysis
CS	Caesarean section
E2	Estradiol
ESHRE	European Society of Human Reproduction and Embryology
FSH	Follicle stimulating hormone
FSHR	Follicle stimulating hormone receptor
fT	Free testosterone
GnRH	Gonadotropin-releasing hormone
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
HIV	Human immunodeficiency virus
hMG	Human menopausal gonadotropin
HRQoL	Health-related quality of life
ICSI	Intracytoplasmatic sperm injection
IR	Insulin resistance
IVF	In vitro fertilization
LBR	Live birth rate
LOD	Laparoscopic ovarian drilling
LMP	Lifestyle modification program
LH	Luteinizing hormone
mFG	modified Ferriman-Gallwey
MMQ	Maudsley Marital Questionnaire
NICE	National Institute for Clinical Excellence
NICU	Neonatal intensive care unit
OD	Ovarian drilling
OHSS	Ovarian hyperstimulation syndrome

OI	Ovulation induction
PCOM	Polycystic ovarian morphology
PCOS	Polycystic ovary syndrome
PCOSQ	PolyCystic Ovary Syndrome Questionnaire
PE	Pre-eclampsia
PR	Pregnancy rate
rFSH	Recombinant follicle stimulating hormone
Ser	Serine
SHBG	Sex hormone-binding globulin
THLOD	Transvaginal hydrolaparoscopic ovarian drilling
uFSH	Urinary follicle stimulating hormone
WHO	World Health Organization

Chapter 1 **INTRODUCTION**

1.1 Definition and prevalence

The polycystic ovary syndrome (PCOS) was first described in 1935 by Stein and Leventhal (Stein and Leventhal, 1935). At that time, the so-called Stein-Leventhal syndrome was characterized by the presence of enlarged sclerocystic ovaries, menstrual irregularity, infertility, hirsutism and obesity (Chamberlain and Wood, 1964; Geisthövel, 2003). Ever since there has been an evolution in the diagnostic criteria of PCOS. The criteria that were captured during the Rotterdam consensus meeting in 2003, enclose most of the PCOS phenotypes and are nowadays internationally applied by gynecologists. Using these criteria, PCOS is diagnosed in the presence of two out of the following three criteria: (1) oligo- or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic aspect of one or both ovaries on ultrasound. Pathologies which present or imitate the same characteristics as PCOS, must be excluded (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). The Rotterdam criteria result in four PCOS phenotypes (**Figure 1**). According to these criteria, the prevalence of PCOS is estimated as high as 10%, making this syndrome one of the most common endocrine disorders in women at reproductive age in the developed world (Broekmans, et al., 2006).

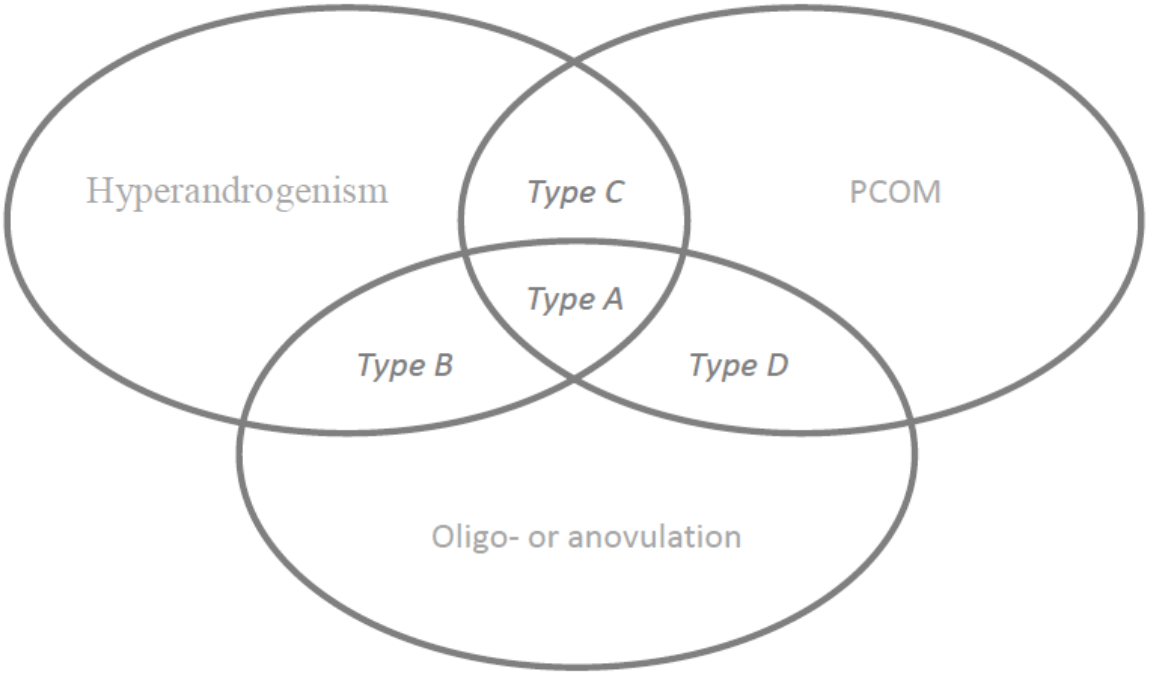


Figure 1: PCOS phenotypes according to the 2003 Rotterdam consensus criteria. Type A = Full-blown PCOS; PCOM = Polycystic ovarian morphology.

1.2 Pathogenesis and pathophysiology

1.2.1 Pathogenesis

The cause of PCOS is still unknown. It is even doubtful if ever one single cause will be found since the pathogenesis is thought to be multifactorial. Endogeneous (e.g., genetic) as well as exogeneous (e.g., life style) factors play an important role in the development and progress of this syndrome (Pasquali et al., 2006; Setji and Brown, 2007). Some believe that a dysfunction in the ovarian steroidogenesis, resulting in androgen excess, is the axis on which the wheel of the vicious PCOS circle turns (Escobar-Morreale and San Millán, 2007; Setji and Brown, 2007; Hirschberg, 2009), while others mention an altered endocrine feedback system or insulin resistance (IR) as the primary defects causing the syndrome (Ching et al., 2007; Hirschberg, 2009).

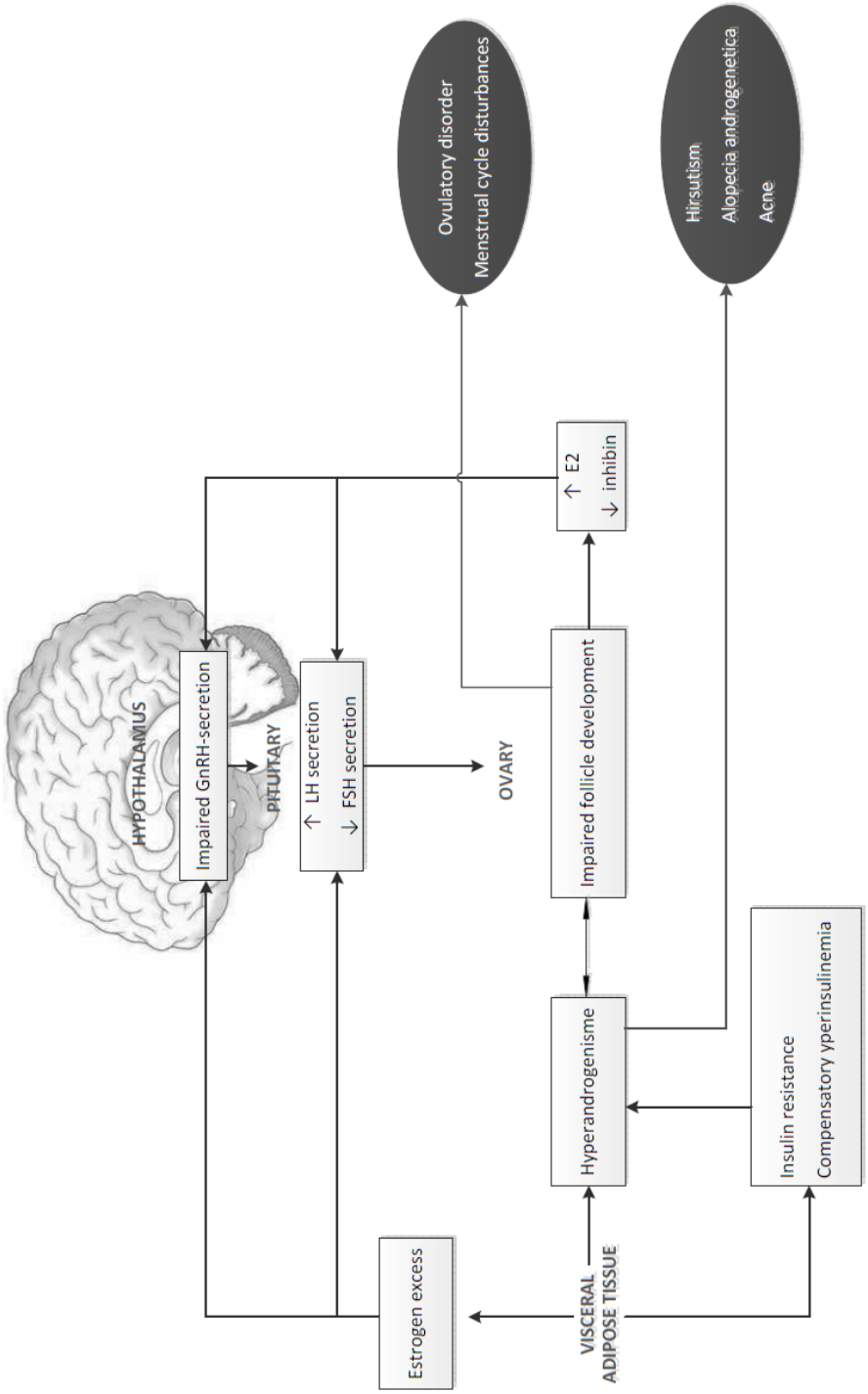
1.2.2 Pathophysiology

The pathophysiology is not fully understood as well. The involvement of many factors make the pathophysiology quite complex (see **Figure 2**).

At the level of the hypothalamic-pituitary axis, an abnormal secretion of gonadotropin-releasing hormone (GnRH) results in an increased secretion of luteinizing hormone (LH) and a relative deficiency of follicle stimulating hormone (FSH) (Hirschberg, 2009). As such, elevated LH:FSH ratios of ≥ 2 are detected in ~50% of the women with PCOS (Banaszewska et al., 2003). These elevated LH:FSH ratios cause an impaired follicle development in one or both ovaries which is characterized by (a) an excessive follicular growth in combination with (b) a poor follicle maturation, (c) a disturbed selection of a dominant follicle, so called “follicular arrest”, and (d) an increased follicular atresia (Jonard and Dewailly, 2004; Hirschberg, 2009). Follicular atresia is characterized by apoptosis of granulosa cells which results in an increased amount of ovarian stroma (Balen et al., 2005; Hirschberg, 2009). Hyperandrogenism is also associated with the impaired LH and FSH secretion. More specifically, the production of androgens (i.e., androstenedione) by the theca cells is increased due to the elevated LH stimulation and an increased amount of ovarian stroma, which is laden by interstitial cells and is responsive to LH, leads to an increased androgen production as well (Balen et al., 2005). On the other hand, androgen excess promotes the process of follicular atresia (Balen et al., 2005). In the mural granulosa cells androstenedione is converted into estradiol (E2) through a process of aromatization (Balen et al., 2005). The rising E2 level, in combination with the higher potency of polycystic ovaries to produce inhibin may be responsible for the impaired endocrine feedback system (Tanabe et al., 1990).

An increased prevalence of IR and compensatory hyperinsulinemia is observed in women with PCOS. Insulin functions as a co-gonadotropin and hence has an influence on the folliculogenesis (Diamanti-Kandarakis and Dunaif, 2012). In women with PCOS the ovarian theca cells seem also more responsive to androgen-stimulating insulin-actions resulting in increased androgen levels (Diamanti-Kandarakis and Dunaif, 2012). Additionally, hyperinsulinemia leads to a decrease of the level of sex hormone-binding globulin (SHBG) which results in an increased level of free testosterone (fT) (Snyder, 2006; Hirschberg, 2009). Taken together, hyperinsulinemia has hence a strengthening effect on the development of hyperandrogenism.

The influence of obesity on the pathophysiology of PCOS is further discussed in Chapter 1.4.


Ovulatory disorder
Menstrual cycle disturbances
Hirsutism
Alopecia androgenetica
Acne
↑ E2
↓ inhibin
HYPOTHALAMUS
Impaired GnRH-secretion
PITUITARY
↑ LH secretion
↓ FSH secretion
OVARY
Impaired follicle development
Hyperandrogenisme
Insulin resistance
Compensatory yperinsulinemia
Estrogen excess
VISCERAL
ADIPOSE TISSUE

1.3 Symptomatology

The pathophysiology results in a very heterogeneous palette of symptoms which differs from person to person and changes over time in terms of type, number and severity of symptoms (Balen et al., 2005; Snyder, 2006; Diamanti-Kandarakis, 2007). Therefore PCOS is often compared to a chameleon which frequently changes color. The first signs of PCOS arise during or just after adolescence and stay until postmenopausal age (Pasquali and Gambineri, 2006; Snyder, 2006; Mani et al., 2014).

The clinical manifestation of PCOS is characterized by polycystic ovaries, menstrual cycle disturbances, hirsutism, alopecia androgenetica, acne, and acanthosis nigricans. Biochemically, elevated levels of LH, (free) testosterone and insulin can be detected. Women with PCOS also often present with **obesity** (see Chapter 1.4).

1.3.1 Polycystic ovarian morphology

The polycystic ovarian morphology (PCOM) is the result of the impaired follicle development leading to an excessive amount of small follicles and ovarian stroma (Hirschberg, 2009). PCOM, as visualized on transvaginal ultrasound, is diagnosed in the presence of ≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 cm^3 in at least one ovary (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004) (**Figure 3**). Although PCOM is prevalent in 20% to 30% of the general female population, not all women present with other features of PCOS (Azziz et al., 2009). In the group of PCOS women, PCOM is estimated to be present in more than 80% of them (Azziz et al., 2009).

Figure 3: Polycystic ovarian morphology on transvaginal ultrasound.

1.3.2 Ovulatory disorder and/or menstrual cycle disturbances

The polycystic ovary syndrome is classified in the World Health Organization (WHO) Group II-category of ovulation disorders which are caused by a dysfunction in the hypothalamic-pituitary-ovarian axis (Brown et al., 2009; National Collaborating Centre for Women's and Children's Health, 2013). Moreover, this syndrome is the most common cause of ovulatory disorders. The absence of ovulation is specifically due to the lack of growth of a dominant follicle which in turn results in no LH surge. The disturbed LH:FSH ratio also leads to an impaired proliferation and secretion of the endometrium. The latter clinically manifests as **menstrual cycle disturbances** which are defined as less than six to eight menstrual bleedings per year with irregular intervals between 35 days and six months (i.e., oligomenorrhea) or intervals of more than or equal to six months (i.e., amenorrhea) (Balen et al., 2005; Macut et al., 2013). Menstrual cycle disturbances are present in 75% to 85% of women with PCOS (Azziz et al., 2009). The menstrual cycle disturbances in women with PCOS often occur after at least one menstrual cycle and are so-called secondary menstrual problems.

The presence of < 10 menstrual cycles per year is mostly used as a criterion to diagnose **ovulatory dysfunction** (i.e., oligo- or anovulatory) (Macut et al., 2013). Still, irregular cycles are not *per se* anovulatory and regular cycles are also not *per se* ovulatory (Azziz et al., 2009). So, one has to keep in mind that using this criterion may lead to a number of false negative and false positive diagnoses (Macut et al., 2013).

Anovulatory subfertility is an important consequence of the ovulatory disorder and is present in 55 to 90% of women with PCOS (Balen et al., 2005; Badawy et al., 2009). The pathophysiologic mechanism that causes oligo- and/or anovulation is explained in Chapter 1.2.2 and 1.3.2. The treatment of anovulatory subfertility is discussed in Chapter 1.6.

1.3.3 Antimüllerian hormone

The antimüllerian hormone (AMH) is a protein that is produced by granulosa cells of small antral follicles (≤ 4 mm) among others (Weenen et al., 2004; Bhide et al., 2015). It serves as a molecular biomarker for the relative size of the ovarian reserve (Weenen et al., 2004). PCOS is associated with an increased concentration of serum AMH (Homburg et al., 2014; Bhide et al., 2015). This can partially be explained by the increased number of small antral follicles. Besides, Bhide et al. (2015) has proven that the AMH production per antral follicle is significantly higher in subfertile women with PCOS when compared with women with PCOM only, and when compared with women without PCOM or PCOS.

AMH is thought to play a role in the pathophysiologic mechanism of anovulation in women with PCOS due to an inhibitory effect of AMH on the actions of FSH (Homburg et al., 2014; Bhide et al., 2015).

1.3.4 Biochemical and clinical hyperandrogenism

1.3.4.1 Biochemical hyperandrogenism

Hyperandrogenemia is the biochemical expression of androgen excess. The causal pathway is explained in Chapter 1.2.2. Free testosterone appears to be the single most predictive marker with ~60% of PCOS women demonstrating supra-normal levels (Huang et al., 2010). The increased bio-availability of androgens to peripheral tissues leads to the well-known clinical signs of androgen excess.

1.3.4.2 Clinical hyperandrogenism

Androgens influence the functioning of the pilosebaceous unit from which both hair follicles and sebaceous glands develop (Balen et al., 2005). Hence, androgens – and especially high levels of androgens - may on the one hand stimulate, and on the other hand inhibit the growth of hair follicles of the sexual type, as well as they may stimulate the development of seborrhea. These mechanisms result in hirsutism, alopecia androgenetica and acne, respectively.

Hirsutism is present in 60-70% of the women with PCOS, making this the most common clinical sign of hyperandrogenemia (Macut et al., 2013). It is defined as the presence of excessive terminal hair growth according to a male-like pattern which is typified by hair on the chin, face, chest, abdomen, back, thighs, and upper arms (Azziz et al., 2009; Yildiz et al., 2010; Macut et al., 2013). At those places androgens stimulate the transformation of fine, unpigmented vellus-like hair into coarse, pigmented, thickened terminal hair (Balen et al., 2005). The widely used method to evaluate the degree of hirsutism is the modified version of the Ferriman-Gallwey scale (mFG scale) assessing the hair growth at nine sites of the body using a 5-point Likert scale (0 = *absence of terminal hair*; 4 = *extensive terminal hair growth*) (Ferriman and Gallwey, 1961; Azziz et al., 2009; Yildiz et al., 2010) (**Figure 4**). A score more than or equal to eight is classified as hirsute (Yildiz et al., 2010).

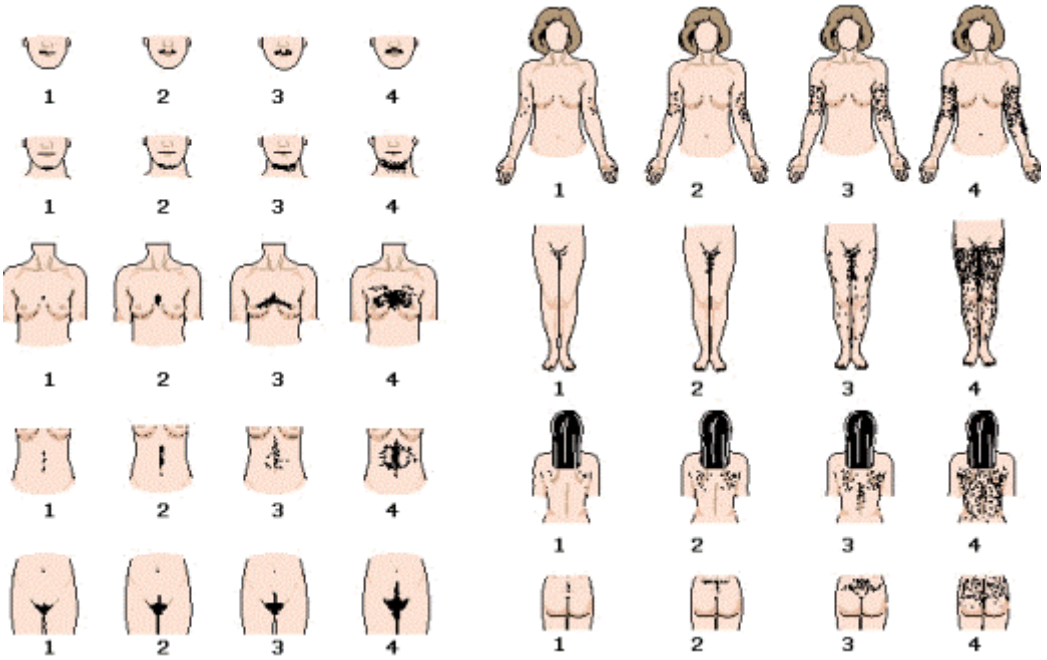


Figure 4: The modified Ferriman-Gallwey scale of hirsutism.

Alopecia androgenetica is described as male pattern baldness which is characterized by hair loss on the frontal and sagittal part of the scalp (Balen et al., 2005). This is due to a shortening of the anagen phase resulting in an advanced conversion of terminal hair to vellus-like hair (Geisthövel, 2003; Balen et al., 2005). The prevalence of alopecia androgenetica in women with PCOS is not completely clear and may vary between 5% and 50% (Azziz et al., 2009).

Acne is estimated to be present in 30% of the women with PCOS. Androgens stimulate the production of sebum and an abnormal keratinization of the pilosebaceous unit (Balen et al., 2005). Together this leads to clogged sebaceous glands, presented as pustules.

1.3.5 Acanthosis nigricans

Acanthosis nigricans is the clinical sign of IR. It is a thickening and dark discoloration of the epidermis in specific body parts such as the posterior neck and the axilla (Shivaprakash et al., 2013). Mani et al. (2015) found a significantly higher prevalence of acanthosis nigricans in South Asian women with PCOS (16.8%) when compared with White women with PCOS (3.1%, $p < 0.001$). On the other hand, in a sample of specific Indian women with PCOS, the prevalence of acanthosis nigricans was 56% (Shivaprakash et al., 2013).

In general, the assessment of most symptoms is subjective and requires an experienced physician as well as the use of standardized techniques and scales. Additionally, the assessment is often hindered by the use of drugs and one has to be aware of racial, ethnic and genetic differences that can modify, for example, the effects of androgens on the skin (Williamson et al., 2001; Balen et al., 2005).

1.4 PCOS and obesity

The prevalence of overweight [body mass index (BMI) of 25-29.9 kg/m²] and obesity (BMI ≥ 30 kg/m²) in women with PCOS is estimated between 30% and 70% *worldwide* making this a substantial health problem in those women (Vrbikova and Hainer, 2009; World Health Organization, 2010). The wide range in the observed prevalence is due to racial, ethnical and cultural differences, as well as to differences in PCOS diagnostic criteria or the used BMI classification. *In Europe*, the prevalence of overweight and obesity (including morbid obesity) in women with PCOS is estimated at 18% and 43%, respectively (Pasquali et al., 2006). In general, the prevalence of obesity in the European female population is found to be 6.2% to 36.5% (Berghöfer et al., 2008).

In women with PCOS, there is, regardless of the degree of overweight, mostly a *central fat distribution* whereby the adipose tissue is disproportionately accumulated in the intra-abdominal visceral depot (Kirchengast and Huber, 2001; Yildirim et al., 2003; Diamanti-Kandarakis, 2007). Therefore this type of obesity is called central, abdominal or visceral obesity. Central obesity in women is diagnosed in the presence of a waist circumference ≥ 80 cm and a waist circumference of > 88 cm is indicative of an increased metabolic risk (Després et al., 2001; Hoeger, 2007; International Diabetes Federation, 2012). When compared with the BMI and the waist to hip ratio, the waist circumference correlates better with the absolute amount of abdominal adipose tissue (Norman et al., 2002). Additionally, measuring the waist circumference is a simple, inexpensive and not time consuming technique.

There is no causal relationship between obesity and PCOS in any direction (Escobar-Morreale et al., 2005; Escobar-Morreale and San Millán, 2007). However it is clear that central obesity has a marked negative influence on the pathophysiology of the syndrome due to the (abnormal) hormonal and metabolic activities of the central fat tissue (Pasquali et al., 2006; Diamanti-Kandarakis, 2007) (see Figure 2). More specifically, the intravisceral adipocytes affect the *insulin activity* and the *steroid metabolism* (Diamanti-Kandarakis, 2007). Concerning the insulin activity, visceral adipocytes in women with PCOS show defects in the transmission of insulin messages rather than a defect in the binding-process of insulin to its receptor (Diamanti-Kandarakis, 2007). This causes a decreased cellular glucose uptake resulting in increased impaired glucose tolerance and compensatory hyperinsulinemia (Gambineri et al., 2002; Diamanti-Kandarakis, 2007; Escobar-Morreale and San Millán, 2007; Hoeger, 2007). Moreover, an increased lipolysis also worsens the degree of IR (Diamanti-Kandarakis 2007). *Concerning the steroid metabolism,* intravisceral adipocytes have the property to convert on the one hand inactive cortisone into metabolically active cortisol and on the other hand weak androgens (i.e., Δ-4 androstenedione) into strong androgens (i.e., testosterone), resulting in increased cortisol and testosterone levels, respectively. Additionally, estrogen (excess), produced by fat tissue among others,

causes an impaired feedback to the pituitary gland and the hypothalamus. Together with the hyperresponsiveness of the pituitary gland to GnRH in women with PCOS, this may result in increased serum LH concentrations and increased LH to FSH ratios (Diamanti-Kandarakis, 2007; Hoeger, 2007; Dafopoulos et al., 2009; Vrbikova and Hainer, 2009).

The negative effects of central obesity on the pathophysiology of PCOS lead to a worse clinical manifestation of the syndrome. As such, obese women with PCOS present with an increased prevalence of hirsutism, menstrual cycle disturbances, anovulatory dysfunction and subsequent fertility problems when compared with normal weight women with PCOS (Gambineri et al., 2002; Laitinen et al., 2003; Pasquali et al., 2006; Diamanti-Kandarakis, 2007; Hoeger, 2007; Hirschberg, 2009). Although, the exact influencing pathway of obesity on the reproductive function in women with PCOS is not completely clear, there is evidence that obese women with PCOS have an increased need for assisted reproductive technology and have a higher incidence of blunted responsiveness to pharmacological ovulation induction (OI) agents (Gambineri et al., 2002; Hirschberg, 2009).

1.5 PCOS and psychological wellbeing

The polycystic ovary syndrome is a trigger for psychological morbidity (i.e., higher depression rate, anxiety) (Jones et al., 2002; Elsenbruch et al., 2003; Snyder, 2006; Jones et al., 2008). In turn, this leads to an increased likelihood of experiencing a reduced health-related quality of life (HRQoL) (Thomson et al., 2010).

1.5.1 PCOS and health-related quality of life

Health-related quality of life is a subjective and multidimensional concept that comprises physical, emotional and social aspects associated with a specific disease or its treatment (Colwell et al., 1998). The HRQoL is an important outcome measure for any patient but it may be particularly of interest in patients with a chronic disease (e.g., PCOS) who must deal with their disease for a long period in time (Trent et al., 2002).

There is evidence that PCOS has a substantial negative influence on a woman's HRQoL (Ching et al., 2007; Jones et al., 2008). As such, the level of HRQoL is found to be lower in women with PCOS when compared with women at reproductive age without PCOS (Elsenbruch et al., 2003; Hahn et al., 2005; Ching et al., 2007). Moreover, Coffey et al. (2006) found that PCOS had a worse impact on patient's psychological well-being than other (chronic) medical conditions (i.e., asthma, epilepsy, diabetes, back pain, arthritis and coronary heart disease), while the impact of PCOS on patient's physical well-being was found to be similar or milder when compared with those other mentioned medical conditions (Coffey et al., 2006). This is striking since the psychological impact of infertility (in general) was found to be similar to the psychological impact associated with other (serious) medical conditions (i.e., heart disease, cancer, hypertension and infection with HIV) (Domar et al., 1993; National Collaborating Centre for Women's and Children's Health, 2013).

1.5.2 PolyCystic Ovary Syndrome Questionnaire

To evaluate women's subjective perception of the influence of specific PCOS characteristics on their level of quality of life, the disease-specific PolyCystic Ovary Syndrome Questionnaire (PCOSQ) was developed (Cronin et al., 1998). This is a patient-generated questionnaire, meaning that the included items are based upon patient interviews rather than upon the clinical opinion of health professionals (Cronin et al., 1998; Guyatt et al., 2004; Coffey et al., 2006). These interviews revealed that emotional wellbeing, body hair, weight, infertility problems and menstrual problems were the most important domains of HRQoL affected by PCOS (Cronin et al., 1998; Jones et al., 2002). This standardized

questionnaire consists of 26 items and each item is scored on a 7-point Likert scale (1 = *high concern*, 7 = *no concern*) (Cronin et al., 1998). Higher scores indicate a qualitatively higher level of HRQoL or a lower level of PCOS-related concern (Cronin et al., 1998). The test-retest reliability is found to be high (intra-class correlation coefficients > .80) and the internal consistency is acceptable to excellent (Cronbach's $\alpha \geq .70$) (Guyatt et al., 2004; Jones et al., 2004; Coffey et al., 2006). The face validity was evaluated by Jones et al. (2004) by performing semi-structured interviews in 12 women with PCOS. They concluded that the validity of the PCOSQ could be improved by the addition of an acne domain to the PCOSQ (Jones et al., 2004). On the other hand, the construct, discriminant and longitudinal validity were confirmed by research (Guyatt et al., 2004; McCook et al., 2005; Coffey et al., 2006). The latter supports the use of this disease-specific questionnaire as an evaluative instrument in clinical trials (Guyatt et al., 2004). This is important because the use of HRQoL as an outcome parameter provides valuable extra information from the patient's perspective about the effectiveness of a treatment (Cronin et al., 1998; Jones et al., 2002).

1.5.3 Influence of PCOS characteristics on HRQoL

Using this standardized questionnaire, several researchers concluded that *weight* (i.e., weight gain and problems to maintain weight at a normal level) is the domain of highest concern in women with PCOS when compared with the other four PCOSQ domains (Guyatt et al., 2004; Jones et al., 2004; McCook et al., 2005; Coffey et al., 2006; Ching et al., 2007). Furthermore, McCook et al. (2005) and Ching et al. (2007) found a significant negative correlation between different BMI classifications and all PCOSQ domain scores on the one hand and between BMI and the weight PCOSQ domain score (r = -.33, p = .001) on the other hand. In contrast, the Hashimoto et al. (2003) study didn't find a significant difference of the body hair, weight, infertility problems and menstrual problems PCOSQ domain score between several BMI categories in a sample of Austrian women. The *reproductive history*, more specifically "the delivery of a viable child", was determined as a significant predictor for the infertility problems PCOSQ subscale score (McCook et al., 2005). But there was no significant correlation between the fertility status and the other PCOSQ subscale scores (McCook et al., 2005). The body hair PCOSQ subscale score was found to be significantly negatively correlated with clinical (i.e., mFG-score) and biochemical (i.e., testosterone) signs of *hyperandrogenism* (McCook et al., 2005; Harris-Glocker et al., 2010; Thomson et al., 2010).

Generally, the observed differential influence and the severity of the influence of PCOS characteristics must be interpreted within a certain socio-cultural and ethnic context (Hashimoto et al., 2003; Schmid et al., 2004).

1.5.4 Influence of PCOS on sexual and relational satisfaction

The polycystic ovary syndrome does not only have an impact on a woman's quality of life, but also affects her concept of self as being a female or feminine based partially on physical characteristics as well as on psychological and social pressure (i.e., gender identity) (Kitzinger and Willmott, 2002). On the one hand, symptoms of PCOS associated with a rather "masculinized" physical appearance (i.e., hirsutism, alopecia androgenetica, acne, overweight) cause body dissatisfaction in women with PCOS (Kitzinger and Willmott, 2002; Snyder, 2006; Jones et al., 2008; de Niet et al., 2010). On the other hand, women with PCOS often can't meet the expected female behavior due to the presence of menstrual disturbances and the inability to conceive a child (Kitzinger and Willmott, 2002; Snyder, 2006). Both factors make them feel different and less feminine when compared with other women without PCOS (Kitzinger and Willmott, 2002; Snyder, 2006).

Given the PCOS symptomatology, one should expect that PCOS women's feeling of reduced femininity may cause problems with her level of sexual functioning and satisfaction. As such, women with PCOS often report to feel less satisfied with their sexual life when compared with women without PCOS (Elsenbruch et al., 2003; Drosdzol et al., 2007; Tan et al., 2008; Månsson et al., 2011). Evidence about the association of specific objective PCOS characteristics with the level of sexual satisfaction in women with PCOS is scarce and conflicting (Elsenbruch et al., 2003; Hahn et al., 2005; Drosdzol et al., 2007; Månsson et al., 2011; Stovall et al., 2012). For example, the mFG-score of hirsutism on the one hand, and the serum testosterone level on the other hand were found to be negatively and not associated, respectively, with PCOS women's level of sexual satisfaction (Drosdzol et al., 2007; Stovall et al., 2012). Also no significant association of the objective presence of acne with the level of sexual satisfaction and sexual functioning of women with PCOS was documented by Hahn et al. (2005) and Stovall et al. (2012). There is conflicting evidence too about the association of PCOS women's BMI with their sexual satisfaction and functioning. Namely, a negative association, on the one hand, and the absence of an association, on the other hand, is described (Elsenbruch et al., 2003; Hahn et al., 2005; Månsson et al., 2011; Stovall et al., 2012). Finally, the presence of a wish to conceive is not related to PCOS women's sexual satisfaction (Tan et al., 2008).

To date, there is no evidence about the association of PCOS women's subjective perception of PCOS with their level of sexual satisfaction. This should however be interesting and valuable information since the subjective perception of a stressor (i.e., PCOS) is theoretically and empirically more directly related to individual and relational well-being than its objective characteristics (Trent et al., 2002; Weber, 2011). Furthermore, a strong association of couple's sexual satisfaction with their level of relational satisfaction is well-documented (Christopher and Sprecher, 2000). Therefore, it might be

interesting to study the association of PCOS characteristics with non-sexual aspects of a long term intimate relationship, like the relational satisfaction.

1.6 Treatment of anovulatory subfertility in PCOS

1.6.1 Weight loss as first-line treatment

The 2013 NICE guidelines recommend infertile anovulatory women with a BMI ≥ 30 kg/m² to first lose weight in order to increase their chance to conceive spontaneously (National Collaborating Centre for Women's and Children's Health, 2013). According to the Thessaloniki consensus, weight loss is also the recommended first-line treatment in overweight and obese women with PCOS (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008).

1.6.1.1 Effect of weight loss on physical parameters

The existing evidence shows that a modest weight loss of 5-10%, regardless of the degree of overweight or obesity, results in an improvement of metabolic and endocrine parameters in women with PCOS. More specifically, an improved insulin sensitivity as well as lower fasting insulin levels, lower LH levels, increased SHBG levels, and decreased fT levels are observed (Huber-Buchholz et al., 1999; Norman et al., 2002). These changes result indirectly in a reduction of hirsutism, an improvement of the menstrual regularity, restoration of ovulation and consequently increases the chance of a spontaneous conception (Huber-Buchholz et al., 1999; Hoeger et al., 2004; Thessaloniki ESHRE/ASRM-Sponsored Consensus Workshop Group, 2008; Thomson et al., 2008).

In order to achieve a modest but sustained effect, the recommended strategy to lose weight is focused on modifying one's lifestyle into a more healthy and regular one. Therefore, a combination of diet, exercise and cognitive-behavioral therapy (CBT) is advised (Norman et al., 2002; Shaw et al., 2005; Hoeger, 2006). The fact that the clinical manifestation of PCOS will probably return or possibly even become worse after weight regain, stresses the importance of a lasting weight loss (Norman et al., 2002). Hence, achievable goals that meet the needs and the capabilities of each individual are crucial (Norman et al., 2002). In women with PCOS, lifestyle modification programs (LMPs) have proven their effectiveness in terms of weight loss, endocrine parameters, menstrual regularity, frequency of spontaneous ovulation, chance of pregnancy and live birth rate (Hoeger et al., 2004; Tang et al., 2006; Thomson et al., 2008). The longest period over which the effectiveness of LMPs has been observed is 48 weeks, but strikingly, also after a shorter time limit of 20 and 24 weeks lifestyle modification had already a positive effect (Tang et al., 2006; Hoeger et al., 2004; Hoeger, 2007; Thomson et al., 2008).

1.6.1.2 Effect of weight loss on HRQoL

Although body weight is the highest concern in women with PCOS and HRQoL is an important marker from the patient's perspective for the efficacy of a treatment, little research has been done using HRQoL as outcome parameter for the efficacy of weight loss interventions in the general population as well as in the specific population of women with PCOS (Jones et al., 2008; Harris-Glocker et al., 2010; Thomson et al., 2010; Lasikiewicz et al., 2014). Some evidence indicates that (a) HRQoL improvements depend on weight losses greater than 5%, and that (b) an even greater improvement is observed when weight loss exceeds 10% of initial body weight (Lasikiewicz et al., 2014).

Till now, only two research groups focused on the effect of lifestyle modification on *HRQoL* in overweight and/or obese women with PCOS (Harris-Glocker et al., 2010; Thomson et al., 2010). More specifically, Harris-Glocker et al. (2010) studied the HRQoL, as measured by the PCOSQ, during a 24-week LMP in a group of obese (BMI > 95th percentile) adolescent (12-18 years) women with PCOS. The LMP consisted primarily of group support by a dietician, psychologist, and structured group exercise, alternated with individual meetings as needed. The results of that study revealed that a treatment of lifestyle modification and oral contraceptives, in combination with or without metformin, had a positive effect on the HRQoL in those women. As such, this indicates that metformin had no additional effect in terms of HRQoL. Despite the significant decrease in BMI in the group with and without metformin (i.e., 4%, p = .008 and 5.2%, p = .001, respectively) and despite the significant increase in all PCOSQ domain scores over the period of 24 weeks, there was only a trend towards a correlation between the decrease in BMI and the increase in HRQoL (r = -0.333, p = .06). Similarly, Thomson et al. (2010) performed a 20-week lifestyle modification treatment in overweight and obese (BMI = 25–55kg/m^2) adult (18-41 years) women with PCOS investigating the additional value of exercise in a program consisting of hypocaloric diet only. The exercise subprogram comprised aerobic exercise or combined aerobic-resistance exercise. The researchers found that lifestyle modification, consisting of diet with or without exercise, had a positive impact on HRQoL in overweight and obese adult women with PCOS. They observed a significant weight loss in all treatment groups ($p \leq .001$), as well as a significant improvement of all PCOSQ domain scores ($p \leq .001$), except for the body hair domain score. A significant correlation between changes in weight and changes in PCOSQ emotion domain scores (r = -.35, $p \leq .01$) and between changes in weight and changes in PCOSQ body weight domain scores (r = -.43, $p \leq .01$) were found.

The latter study indicates that exercise has no added value to diet only in terms of HRQoL. Although, when investigating the isolated effect of exercise on body image distress, Liao et al. (2008) found that a self-directed walking program significantly reduced the level of body image distress in overweight and obese women with PCOS. Furthermore, the effectiveness of diet in terms of depression rate and level of self-esteem is proven to depend on the diet composition (Galletly et al., 2007). Concerning

psychological support, Shaw et al. (2005) has proven that the addition of CBT to a multi-component LMP is important to obtain a maximum effect in terms of weight loss. To date, there is no evidence about the effect of psychological interventions on the psychological well-being of women with PCOS. Since HRQoL is an important marker from the patient's perspective for the efficacy of a treatment, additional research on this topic is needed (Cronin et al., 1998; Jones et al., 2008). Moreover, as earlier studies have not accounted for the influence of acne on women's HRQoL it is of interest to evaluate this when studying HRQoL in women with PCOS (Jones et al., 2004).

1.6.2 Pharmacological and surgical treatment

The essence of a pharmacological treatment of anovulatory subfertility is OI through indirect influence of the hypothalamic-pituitary axis or via directly increasing the circulating FSH level (Balen et al., 2005). Due to the disturbed gonadotrophic environment, the number of available FSH-sensitive antral follicles is larger in a polycystic ovary compared to a normal ovary. Subsequently those ovaries are especially prone to excessive multiple follicle development.

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008) and the National Collaborating Centre for Women's and Children's Health (2013) recommend a treatment with clomiphene citrate (CC) as the first-line treatment for OI in PCOS. Nevertheless, a treatment with low-dose FSH is also described as a possible first-line treatment (see Chapter 1.6.2.2 Gonadotropin therapy).

1.6.2.1 Clomiphene citrate

Clomiphene citrate is a selective estrogen receptor modulator. It blocks the binding of circulating E2 to the oestrogen receptors in the hypothalamus by attaching itself to those receptors. This causes a loss of feedback from circulating E2 and restores the pituitary secretion of LH and FSH (McDowell et al., 2013). As such, CC has an indirect effect on the ovarian function.

Clomiphene citrate is administered from day 3 to 7 of a spontaneous or induced menstrual bleeding, with a starting dose of 50 mg/day and a maximum dose of 150 mg/day (Balen et al., 2005). It is advised to administer this drugs for no longer than 6 cycles. Although, monitoring the ovarian response through ultrasound is required, the prevalence of the ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies after a treatment with CC is rather rare (van Wely et al., 2004; Balen et al., 2005; National Collaborating Centre for Women's and Children's Health, 2013).

About 15-20% of the subfertile women with PCOS are "clomiphene resistant", meaning that they do not respond to a maximum daily dose of 150 mg CC/day for 5 subsequent days in the early follicular phase (Nugent et al., 2000; Bayram et al., 2004; Farquhar et al., 2004; van Wely et al., 2004; Balen et al., 2005; Farquhar et al., 2012). The exact cause of CC resistance is largely unknown but several factors have been suggested to influence the response to CC (Overbeek et al., 2009). As such, obesity and hyperandrogenism were associated with a decreased ovulation rate after OI with CC (Imani et al., 2000). The response to CC seems also mediated by the sensitivity of the FSH receptor (FSHR). More specifically, a Ser680Ser-polymorphism of the FSHR gene is associated with a low sensitivity of the FSHR for FSH that makes it incapable to respond adequately to the raised FSH levels in OI therapy (Overbeek et al., 2009).

The two alternative treatments currently used for OI in these women are, on the one hand, gonadotropin therapy and, on the other hand, ovarian drilling (OD) (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008; Farquhar et al., 2012; National Collaborating Centre for Women's and Children's Health, 2013).

1.6.2.2 Gonadotropin therapy

The principle of gonadotropin therapy is direct ovarian stimulation using human menopausal gonadotropin (hMG), or either urinary (uFSH) or recombinant FSH (rFSH) (van Wely et al., 2003; Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008; Farquhar et al., 2012). Human menopausal gonadotropin contains equal amounts of LH and FSH, while LH is absent in uFSH and rFSH (van Wely et al., 2003).

In general, gonadotropin therapy increases the risk of multiple follicle development, multiple pregnancies (about 20%), OHSS and cyst formation (Nugent et al., 2000; Farquhar et al., 2002; Farquhar et al., 2004; Balen et al., 2005; Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008; Farquhar et al., 2012). In order to achieve a more controlled follicle stimulation and to avoid these iatrogenic risks several dose regimens (i.e., low-dose step-up and low-dose step-down regimen) have been used in combination with intensive ultrasound and endocrine monitoring (i.e., E2) (Christin-Maitre and Hugues, 2003; van Wely et al., 2003; Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). The prospective, randomized multicentric study by Christin-Maitre and Hugues (2003) showed that a low-dose step-up protocol was the most efficient and safest for use.

As mentioned in the introduction of this chapter (see Chapter 1.6.2.), gonadotropin therapy is not only a second-line treatment in case of "clomiphene resistance", but is also a possible first-line OI treatment in women with PCOS. Moreover, Homburg et al. (2012) has proven that the reproductive outcome after OI with low-dose FSH is significantly better than after OI with CC, with respect to clinical pregnancy rate (PR) and live birt rate (LBR) per (first) cycle, cumulative clinical PR and LBR over three cycles and time-to-pregnancy. The low-dose FSH treatment was also not associated with anti-endometrial effects when compared with CC treatment (Homburg et al., 2012).

1.6.2.3 Ovarian drilling

Ovarian drilling is a procedure that creates multiple holes in the ovarian cortex and stroma by laser vaporization or electrocoagulation (Farquhar et al., 2012). The mechanism of OD is generally unknown but it is thought that this procedure destroys ovarian androgen-producing tissue and decreases the

peripheral conversion of androgens to estrogens (Hendriks et al., 2007; Gordts et al., 2009; Farquhar et al., 2012). Hence disturbances of the ovarian-pituitary feedback mechanism are corrected and the hormonal environment is restored (Hendriks et al., 2007; Gordts et al., 2009; Farquhar et al., 2012).

To date, there is no consensus about the number of punctures to perform per ovary in order to achieve an optimal effect. A retrospective study by Amer et al. (2002) showed that performing three punctures per ovary is sufficient to achieve a significant higher ovulation and pregnancy rate when compared with ≤ 2 punctures per ovary ($p < .05$ and $p < .05$, respectively). On the other hand, the prospective randomized study by Tabrizi et al. (2005) concluded that a 15-point electrocauterization is significantly more effective than a 5- or 10-point electrocauterization in terms of 12-month pregnancy and live birth rate ($p = .016$ and $p = .004$, respectively). In 2008, the Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group agreed upon the fact that > 10 punctures per ovary should be discouraged because of the risk of excessive (permanent) ovarian tissue damage, peri-adenexal adhesions and the association with premature ovarian failure (Weerakiet et al., 2007; Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). Yet, the degree of ovarian tissue damage not only depends on the number of punctures but is also related to the used technique (i.e., monopolar and bipolar coagulation, laser vaporization, or ovarian biopsies) (Hendriks et al., 2010). It has been proven that bipolar electrocoagulation resulted in significantly more destruction per burn than the CO_2 laser and monopolar electrocoagulation technique (Hendriks et al., 2010).

Two methods for performing an OD are described depending on the surgical procedure: (a) laparoscopic ovarian drilling (LOD) and (b) transvaginal hydrolaparoscopic ovarian drilling (THLOD). Laparoscopic ovarian drilling was first described by Gjönnaess in 1984 (Gjönnaess, 1984). Ovarian drilling through this method has been proven to have a positive effect on consecutive spontaneous ovulations (80%) and conception (61%) rates, as well as on the ovarian responsiveness to OI agents (Amer et al., 2002; Farquhar et al., 2002; Nahuis et al., 2011; Farquhar et al., 2012). This technique also has the advantage to avoid OHSS and multiple pregnancies (Farquhar et al., 2002). Moreover, the positive effect of LOD seems to last for at least 12 months after surgery (Kovacs and Norman, 2007; Nahuis et al., 2011). But, one has to keep in mind that LOD is an invasive procedure which possibly brings along short and long term complications due to surgery and anesthetics (Farquhar et al., 2002; Farquhar et al., 2004; Balen et al., 2005).

On the other hand, THLOD is a less invasive procedure when compared with LOD and is associated with a low risk of intra- and postoperative complications. The effectiveness of THLOD in terms of ovulation and pregnancy rate is also described to be similar to LOD (Fernandez et al., 2001; Shibahara

et al., 2006; Badawy et al., 2009; Gordts et al., 2009; Catenacci and Goldberg, 2011). Nevertheless, the latter needs to be confirmed by long term research.

1.6.2.4 Cost-effectiveness of gonadotropin therapy versus ovarian drilling in clomiphene resistant women

Till now, the cost-effectiveness of gonadotropin therapy has only been compared with the laparoscopic method of ovarian drilling. Three cost-effectiveness analyses (CEAs) comparing gonadotropin therapy with LOD in CC resistant women with PCOS were published (Farquhar et al., 2004; van Wely et al., 2004; Nahuis et al., 2012). Farquhar et al. (2004) (n = 50) performed a prospective CEA alongside a randomized controlled trial and concluded that LOD without additional drug treatment was the most cost-effective option from the societal perspective in terms of cost per pregnancy and cost per live birth over a time period of 6 months. Since no multiple pregnancies occurred in both treatment groups a cost for multiples pregnancies was not taken into account when calculating the cost per live birth. In contrast to these results, van Wely et al. (2004) (n = 168), who performed a prospective CEA alongside a multicentre randomized clinical trial, found a comparable cost-effectiveness from the societal perspective of both treatments over a time period of 12 months in terms of the mean total cost per woman until an ongoing pregnancy. The LOD strategy was followed by a treatment with CC or rFSH if anovulation persisted for 8 weeks or when patients became anovulatory again after LOD. Besides those two short term CEAs, Nahuis et al. (2012) performed a CEA alongside a long term follow-up study over a period of 8 to 12 years. In this study, only the cost for the public payer was considered. The authors concluded that LOD was the most cost-effective option when looking into the cost per (first) live birth, including costs until 6 weeks after delivery.

In conclusion, current evidence on the cost-effectiveness of gonadotropin therapy and LOD in CC resistant women with PCOS is scarce, conflicting, and performed from different health-economic perspectives and over different lengths of time. Moreover, a CEA from the societal perspective based on real-life data is missing.

1.7 PCOS and pregnancy, delivery and neonatal outcome

The risk of an adverse pregnancy, delivery and neonatal outcome is increased in women affected by PCOS. There is evidence that women with PCOS are at increased risk of a (recurrent) miscarriage, which might be linked to pre-pregnancy LH hypersecretion, hyperandrogenemia, hyperinsulinemia and/or thrombophilia (Regan et al., 1990; Okon et al., 1998; Wang et al., 2001; Kazerooni et al., 2013).

Furthermore, an ongoing pregnancy in women with PCOS is often complicated by pregnancy induced hypertension, pre-eclampsia (PE) and gestational diabetes mellitus (GDM) (Altieri et al., 2010). GDM in PCOS is the result of a state of IR as induced by the pregnancy itself, in combination with a predisposition of glucose-intolerance in women with PCOS (Altieri et al., 2010; Mikola et al., 2001; Turhan et al., 2003). Pre-eclampsia in women with PCOS may be caused by low levels of insulin-like growth factor binding globulin-1 which is a regulator of the insulin-like growth factor-1 activity (Altieri et al., 2010; Kjerulff et al., 2011).

These pregnancy complications give directly or indirectly rise to an increased risk of preterm delivery, Caesarean section (CS) or assisted vaginal delivery (Altieri et al., 2010). The new-born babies stay more frequently in a neonatal intensive care unit (NICU) and the perinatal mortality is also higher (Boomsma et al., 2006; Qin et al., 2013).

1.7.1 Influence of overweight on pregnancy, delivery and neonatal outcome in women with PCOS

In the general population, multiple studies have focused on the association of pre-pregnancy maternal overweight and obesity with the obstetric and neonatal outcome. As such, there is evidence showing an increased risk of GDM, PE, CS, instrumental delivery, postpartum haemorrhage, infection, prolonged hospital stay, congenital malformations, macrosomia and an increased NICU admission in overweight and obese women (Sarwer et al., 2006; Heslehurst et al., 2008; Poobalan et al., 2009; Blomberg, 2013; Cnattingius et al., 2013; Wahabi et al., 2014). Considering the risk of preterm birth in overweight and obese women, the evidence is conflicting. Some studies indicate an association of an increase of the BMI with an increase of the risk of preterm birth (< 37 weeks gestation) (Khatibi et al., 2012; Cnattingius et al., 2013). On the other hand, the systematic review and meta-analysis of McDonald et al. (2010) reports no association of overweight and obesity with an increased risk of preterm birth. Also, Nohr et al. (2007) found no increased risk of induced preterm birth in obese women (BMI ≥ 30 kg/m²). However, this was only the case after adjustment for obesity-related diseases (such as PE, hypertension and diabetes mellitus). Pre-pregnancy maternal obesity also has been associated with an increased risk of preterm birth, GDM and stillbirth specifically in twin

pregnancies (Salihu et al., 2010; Simões et al., 2011; Dickey et al., 2012; Dickey et al., 2013). Additionally, an excessive gestational weight gain (GWG) is described to have an additional deleterious effect on the risk of PE, CS, macrosomia and postpartum weight retention in singleton and twin pregnancies in obese women (Cedergren, 2006; Nohr et al., 2008; Bogaerts et al., 2012; Gavard and Artal, 2014).

On the other hand, the existing evidence about the influence of overweight and obesity on the pregnancy, delivery and neonatal outcome in women with PCOS is scarce and not unambiguous. A few retrospective studies investigating the pregnancy, delivery and neonatal outcome in women with PCOS versus women without PCOS have adjusted their analyses for BMI (Mikola et al., 2001; Turhan et al., 2003). Based on the results of those multivariate analyses, pre-pregnancy overweight (BMI > 25 kg/m²) was found to be an important predictor of GDM (Mikola et al., 2001; Turhan et al., 2003). In contrast, de Wilde et al. (2014) – who studied preconception predictors of GDM – concluded that BMI, waist circumference and waist/hip ratio were no significant predictors of GDM in adult women with PCOS.

Han et al. (2011) studied the influence of overweight (BMI > 25kg/m²) on the pregnancy outcome in Asian women with PCOS. Using a case-control design of overweight versus normal weight women, their results showed a significantly increased prevalence of GDM and fetal macrosomia in overweight women with PCOS when compared with normal weight women with PCOS ($p < .014$ and $p < .001$, respectively).

1.8 Aim of this dissertation and methodology

The general objective of this dissertation is to do research about psychological, perinatal, lifestyle and health-economic aspects of the polycystic ovary syndrome that really matter for the patient, her family and the society.

More specifically, the following research questions are studied:

1) How are objective PCOS characteristics and PCOS-related concerns associated with the level of sexual and relational satisfaction of women with PCOS and their partners?

   A cross-sectional study is set up and a validated questionnaire (i.e., the Maudsley Marital Questionnaire; MMQ) is used to measure the level of sexual and relational satisfaction of women with PCOS as well as of their partner. Dyadic statistical analyses are performed to take into account the interdependence of both partners in a couple and to explore potential differences between partners in the association of subjective and objective PCOS characteristics with the satisfaction level (Chapter 3).

2) What is the influence of overweight on the pregnancy, delivery and neonatal outcome in women with PCOS?

   A retrospective comparative cohort study is set up and multivariate statistical analyses are performed in order to investigate the influence of overweight and to take into account the possible influence of several confounding variables (Chapter 4).

3) What is the evolution of the HRQoL and the BMI of overweight adult women with PCOS during a 24-week lifestyle modification program?

   A 24-week lifestyle modification program, consisting of an individualized diet, exercise and psychological subprogram is set up for overweight (BMI ≥ 25 kg/m²) adult (age of 18-43 years) women with PCOS. Using a prospective within-patient design, changes in BMI and HRQoL of those women are evaluated. The PCOSQ is used to measure the perceived level of HRQoL and an acne parameter is included to evaluate the influence of acne on the perceived level of HRQoL (Chapter 5).

4) What is the cost-effectiveness of gonadotropin therapy and LOD in clomiphene citrate resistant women with PCOS?

A retrospective CEA comparing gonadotropin therapy with LOD in CC resistant women with PCOS is performed using a societal approach. As such, the total cost covered by the society is studied, including (a) the cost covered by the public payer (i.e., direct medical cost), (b) the cost covered by the patient (i.e., direct medical cost and transportation cost), and (c) the costs related to productivity loss . Effectiveness of treatment is expressed in ongoing pregnancy rate and number of live-born children (Chapter 6).

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Chapter 2 SEXUAL AND RELATIONAL SATISFACTION IN COUPLES WHERE THE WOMAN HAS POLYCYSTIC OVARY SYNDROME: A DYADIC ANALYSIS

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Hum Reprod 2015;30:625-631. Epub 2014 Dec 22. Doi: 10.1093/humrep/deu342.

Abstract

Study question: How are objective characteristics of the polycystic ovary syndrome (PCOS) and PCOS-related concerns associated with the sexual and relational satisfaction of PCOS women and their partners?

Summary answer: Both objective PCOS characteristics (parity, women's body mass index (BMI) and current unfulfilled wish to conceive) and PCOS-related concerns (women's infertility-related and acne-related concerns) were associated with sexual and/or relational satisfaction, although some associations differed for PCOS women and their partners.

What is known already: There is some evidence indicating an association between objective PCOS characteristics and sexual satisfaction of PCOS women, but this evidence is conflicting, scarce, and often no validated questionnaires are used to evaluate sexual satisfaction. No evidence is available about the association of (i) PCOS with relational satisfaction; (ii) PCOS-related concerns with sexual and relational satisfaction; and (iii) PCOS with sexual and relational satisfaction as experienced by partners of PCOS women.

Study design, size, duration: We set up a cross sectional study from April 2007 till April 2009 including 31 overweight (BMI ≥ 25 kg/m²) women with PCOS at reproductive age as well as their partners with who they had a committed intimate relationship at the time of recruitment.

Participants/materials, setting, methods: The study was performed at the fertility center of the Ghent University Hospital. Objective PCOS characteristics were registered and PCOS-related concerns were evaluated by the PCOS Questionnaire. Sexual $_{(SS)}$ and relational $_{(RS)}$ satisfaction were measured by the Maudsley Marital Questionnaire (MMQ). Dyadic statistical analyses were performed using linear mixed models ($\alpha < 0.05$).

Main results and the role of chance: A lower parity tended to be associated with higher levels of sexual and relational satisfaction, with a significantly stronger association in PCOS women than their partners ($p_{(SS)} = .015$ and $p_{(RS)} = .009$). A higher BMI tended to be associated with lower and higher satisfaction levels (sexual and relational) in PCOS women and their partners, respectively, with a significantly stronger association in the partners ($p_{(SS)} = .029$ and $p_{(RS)} = .021$). The presence of a current unfulfilled wish to conceive and a higher level of infertility-related concerns was significantly stronger associated with a higher level of PCOS women's relational satisfaction than their partners' ($p_{(RS)} = .021$ and $p_{(RS)} = .011$, respectively). And higher levels of acne-related concern were significantly associated with lower levels of sexual satisfaction in PCOS women ($p_{(SS)} = .025$) and their partners ($p_{(SS)} = .002$).

Limitations, reasons for caution: The fact that this study was performed in a sample of PCOS women who were all overweight and the small sample size are important limitations. Data were partially missing in some couples but this limitation was dealt with by using linear mixed models.

Wider implications of the findings: Our results suggest a differential association of PCOS with sexual and relational satisfaction between PCOS women and their partners. This should be kept in mind during the psychological guidance of couples dealing with PCOS.

Introduction

The polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age (Broekmans et al., 2006). It is characterized by menstrual disorders, anovulatory subfertility, hirsutism, acne, biochemical signs of hyperandrogenism, obesity and insulin resistance (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004; Drosdzol et al., 2007). Due to these characteristics, PCOS is found to be a trigger for psychological morbidity, with PCOS women reporting to feel different, less feminine, and more depressed when compared with non-PCOS women (Elsenbruch et al., 2003; Snyder, 2006; Jones et al., 2008). There is also preliminary evidence that PCOS characteristics negatively affect various aspects of women's sexual life. More specifically, PCOS women often report to feel less attractive and to be less sexually satisfied when compared with non-PCOS women (Elsenbruch et al., 2003; Drosdzol et al., 2007; Tan et al., 2008; Månsson et al., 2011).

Although these results are promising, existing research on how PCOS affects women's sexual and intimate relationships is limited in several ways. Firstly, findings from studies on the specific objective characteristics of PCOS that affect women's level of sexual satisfaction appear to be contradictory. More specifically, indicators of hyperandrogenism were found to have a negative effect (i.e. Ferriman-Gallwey score of hirsutism) in the Drosdzol et al. (2007) study but no effect (i.e. self-reported state of hirsutism and total serum testosterone) in the Stovall et al. (2012) study on PCOS women's sexual satisfaction. Similar conflicting evidence has been found for the association of PCOS women's body mass index (BMI) with their sexual satisfaction and functioning (Elsenbruch et al., 2003; Hahn et al., 2005; Månsson et al., 2011; Stovall et al., 2012). Secondly, previous PCOS-studies focusing on sexuality relied on questionnaires that were often not psychometrically validated. Also, sexual satisfaction was at times measured by means of questionnaires evaluating women's sexual functioning, rather than satisfaction, and including only some items pertaining to their level of sexual satisfaction (Elsenbruch et al., 2003; Hahn et al., 2005; Drosdzol et al., 2007; Tan et al., 2008; Månsson et al., 2011). Thirdly, studies to date did not examine how women's subjective experience of PCOS-related characteristics is related to their sexual life. This is surprising, as a stressor's (like PCOS) objective characteristics need to be conceptually and methodologically differentiated from a person's perception of and reaction to a stressor; moreover, the perception of a stressor is theoretically and empirically more directly related to individual and relational well-being than its objective characteristics (Weber, 2011). Fourthly, as existing research on PCOS and sexual satisfaction/functioning exclusively focused on the perspective of PCOS women, little is known about how partners of PCOS women experience their intimate relationship. Finally, previous studies limited their scope to sexual satisfaction whereas they did not investigate how PCOS affects other non-sexual aspects of long-term intimate relationships, like a couple's level of relational satisfaction. The latter refers to how good or bad couples judge their

intimate relationship to be, and reflecting partners' feelings of mutual understanding, tensions in the relationship, their commitment to the relationship, etc. (Bradbury & Karney, 2010). Furthermore, couple's relational satisfaction correlates strongly with their level of sexual satisfaction (Christopher & Sprecher, 2000; Sprecher & Cate, 2004).

Sexual as well as relational satisfaction are essential characteristics of intimate relationships, and important predictors of both relationship stability and partner's subjective well-being (Bradbury & Karney, 2010). Given its symptomatology, PCOS is assumed to be a chronic stressor for couples to deal with, and to have the potential to undermine both partners' sexual and relational satisfaction. In order to develop evidence-based psychological interventions for PCOS women and their partners, research on the intimate life of couples facing PCOS is essential. Therefore, the present study examined how (i) both objective PCOS characteristics and PCOS-related concerns relate to (ii) sexual as well as relational satisfaction, of (iii) PCOS women and their intimate partner. As a point of major empirical and clinical interest, we also explored potential differences between PCOS women and their partners in the association between PCOS characteristics on the one hand and sexual and relational satisfaction on the other hand, by performing dyadic statistical analyses. Psychometrically validated questionnaires were used to assess all the variables included in the current study.

Materials and methods

We set up a cross sectional study at the Department of Reproductive Medicine of the Ghent University Hospital from April 2007 till April 2009. This study was performed in the context of a lifestyle modification program for overweight women with PCOS between the age of 18 and 43 years old (n = 33). The PCOS women who were involved in a committed intimate relationship at the start of that program (n = 31) were eligible for the current study. At the start of the lifestyle modification program, all 31 PCOS women as well as their partners were informed about the current study by the treating physician and all agreed to participate. PCOS was diagnosed by a gynecologist according to the Rotterdam criteria (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004).

Objective characteristics of PCOS

Overweight was diagnosed as a BMI of ≥ 25 kg/m² (WHO, 2010). Clinical hyperandrogenism was diagnosed by evaluating the presence of visible hair growth and facial acne. The degree of visible hair growth was indicated by the modified Ferriman-Gallwey (mFG) scale and women were classified as hirsute when they had an mFG-score ≥ 8 (Ferriman & Gallwey, 1961; Yildiz et al., 2010). The acne parameter was evaluated by asking women whether facial acne was present or not. Hyperandrogenemia was diagnosed by the presence of a free testosterone (fT) level > 0.50 ng/dL, which was determined at Day 2 or 3 of a spontaneous or induced menstrual cycle. The menstrual cycle was categorized as irregular in case of no menstrual bleeding for > 35 days or > 6 months. Parity and gravidity, both indicators of subfertility, were registered and women were also asked if they had a current unfulfilled wish to conceive.

PCOS-related concerns

To evaluate women's subjective PCOS-related concerns, the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) and an acne Visual Analogue Scale (VAS) were used (Cronin et al., 1998; Guyatt et al., 2004). All PCOS women were given basic instructions to fill out the questionnaire around their first consultation in the lifestyle modification program. The 26-item PCOSQ consists of five domains: emotions (e.g., 'being worried about having PCOS' or 'having a low self-esteem as a result of having PCOS'), body hair, weight, infertility problems and menstrual problems. Each item of the questionnaire was scored on a 7-point Likert scale (1 = *high concern*, 7 = *no concern*), with higher scores corresponding with lower levels of PCOS-related concern (Cronin et al., 1998). For each PCOS woman, the mean score of all domain-specific items and the mean score of the five domain scores generated the score of each PCOSQ domain and the total PCOSQ score, respectively. Whereas, in the original version of the PCOSQ, a time frame of 2 weeks is chosen for PCOS women to report their subjective

experience of PCOS (Cronin et al., 1998), the current study used a time frame of 6 months in order to have a view on the patient's subjective experience of PCOS over a larger period of time. In the current study, the total PCOSQ scale and the 5 separate PCOSQ domain scales showed acceptable to excellent reliability (Cronbach's alpha's between .61 and .95). In order to evaluate the subjective experience of the presence of facial acne, PCOS women indicated to what extent the presence of facial acne influenced their quality of life on a VAS (0 = *no influence*, 10 = *great influence*). Contrary to the PCOSQ scores, higher VAS scores reflect higher levels of acne-related concern.

Sexual and relational satisfaction

Sexual and relational satisfaction of PCOS women and their partners were assessed by means of the Maudsley Marital Questionnaire (MMQ; Arrindell et al., 1983). The MMQ was filled out by the PCOS women as well as by their partners around their first consultation in the lifestyle modification program. The MMQ includes 20 items, each rated on a 9-point Likert scale that ranges from 0 = *high satisfaction* to 8 = *low satisfaction.* The sexual satisfaction subscale and the marital satisfaction subscale were used to assess each participant's subjective evaluation of their sexual life and intimate relationship, respectively. Subscale-scores were calculated separately for the PCOS women and their partners by computing the sum of their responses on all items in the respective subscales. Scores on the sexual satisfaction subscale could range from 0 to 40 and on the marital satisfaction subscale from 0 to 80, with higher scores reflecting lower levels of satisfaction. The psychometric qualities of the Dutch version of the MMQ are confirmed (Arrindell et al., 1983; Arrindell & Schaap, 1985; Joseph et al., 2007). In this study, Cronbach's alpha's were adequate to good (between .70 and .84) indicating an acceptable internal consistency for all the subscales.

Ethical consent

This study has been authorized by the Ethics Committee of the Ghent University Hospital. Couples gave their written informed consent for participation and follow-up.

Statistical analysis

The association between PCOS characteristics on the one hand, and sexual satisfaction $_{(SS)}$ and relational satisfaction $_{(RS)}$ of PCOS women and their partners on the other hand, was analyzed by using linear mixed models (LMM). Dyadic analyses were performed to take into account the interdependence of both partners in a couple and to explore potential differences between partners in the association of PCOS characteristics with satisfaction. For each outcome variable separately, a mixed model accounting for the correlation within dyads was fitted. Models with objective predictors (i.e. objective PCOS characteristics) and subjective predictors (i.e. PCOS-related concerns) separately

were built using forward-stepwise regression. For each of the predictors we allowed for a different association for the PCOS women and their partners. Couples with a missing outcome in one of the partners were included in the LMM analysis, but missingness in the predictors implied the deletion of the data from that couple. Effect sizes reflecting the effect of each predictor on the PCOS woman's and their partner's outcome together were calculated using Cohen's f^2 (Selya et al., 2012). f^2 effect sizes of 0.02, 0.15, and 0.35 are termed *small*, *medium*, and *large*, respectively. The MMQ sexual and relational satisfaction subscale scores of both PCOS women and their partners were compared with published normative data from a sample of heterosexual, married adults (Joseph et al., 2007) by means of a one-sample t-test. The LMM analyses, including the calculation of the effect sizes, were performed using SAS version 9.3. All other statistical analyses were performed using SPSS version 22.0. The statistical significance level was set at $\alpha < 0.05$.

Results

Descriptive statistics

The PCOS women and their partners had an average age of 30.1±5.1 and 34±6.3 years respectively (p = .01). The median length of their relationship was 63 (IQR 89.7) months and 20/31 (64.5%) were married. One couple was lesbian.

The values for objective PCOS characteristics, PCOS-related concerns (reported by PCOS women), as well as sexual/relational satisfaction (reported by both partners) are presented in Table I. Ninety percent (28/31) of the PCOS women filled out the PCOSQ. The response rate on the MMQ was 27/31 (87.1%) and 24/31 (77.4%) for PCOS women and their partners, respectively. The MMQ sexual and relational satisfaction subscale-scores were significantly higher in PCOS women in comparison to their partners ($p_{(SS)}$ = .017 and $p_{(RS)}$ = .007). There was a significant positive correlation for sexual and relational satisfaction between PCOS women and their partners (r = .83, p < .001 and r = .88, p < .001, respectively).

Dyadic analyses

When testing for the association of objective PCOS characteristics with participants' level of sexual and relational satisfaction, the following results emerged (Table II): Firstly, a lower parity tended to be associated with higher levels of sexual and relational satisfaction in both PCOS women and their partners. However, this association was significantly stronger for PCOS women than for their partners ($p_{(SS)}$ = .015 and $p_{(RS)}$ = .009). Secondly, a higher BMI of PCOS women tended to be associated with lower levels of sexual and relational satisfaction of PCOS women, whereas a higher BMI of PCOS women tended to be associated with higher levels of sexual and relational satisfaction of their partners. This association of BMI was significantly different between the PCOS women and their partners ($p_{(SS)}$ = .029 and $p_{(RS)}$ = .021). Thirdly, the presence of a current unfulfilled wish to conceive tended to be associated with higher levels of relational satisfaction in both PCOS women and their partners. This association was significantly stronger in PCOS women than their partners ($p_{(RS)}$ = .021).

Analyses for the PCOS-related concerns – as reported by PCOS women – (see Table II) revealed that higher levels of infertility-related concern were significantly associated with higher levels of relational satisfaction in PCOS women ($p_{(RS)}$ = .028). Higher levels of infertility-related concern also tended to be associated with higher levels of relational satisfaction in the partners of PCOS women. This association was significantly stronger in PCOS women than their partners ($p_{(RS)}$ = .011). Finally, higher levels of acne-related concern were significantly associated with lower levels of sexual satisfaction of PCOS

women ($p_{(SS)}$ = .025) and their partners ($p_{(SS)}$ = .002). This association was not significantly different between PCOS women and their partners.

The effect sizes for all the associations discussed above can be considered as at least medium, except for the association of subjective acne-related concern with sexual satisfaction (see Table II).

Comparison of participants' sexual/relational satisfaction scores with normative data

Joseph et al. (2007) reported a mean (± standard deviation) MMQ sexual and relational satisfaction subscale score of 9.15 (± 7.25) and 14.91 (± 11.76), respectively for a sample of heterosexual, married women (n = 396). For heterosexual, married men (n = 391) the scores were 8.18 (± 7.14) and 12.24 (± 9.54), respectively (Joseph et al., 2007).

In our study, sexual satisfaction levels of the PCOS women and their partners (figures see Table I) tended to be lower (p = 0.7) and higher (p = 0.7), respectively, when compared with that reference sample. Relational satisfaction levels of the PCOS women and their partners were significantly higher (p = 0.01 and p = 0.002, respectively) when compared with that reference sample.

Discussion

In the current study, we investigated the association of PCOS (i.e. objective PCOS characteristics and PCOS-related concerns) with the sexual and relational satisfaction of couples dealing with PCOS, as well as differences in those associations between PCOS women and their partners. Our results suggest that objective PCOS characteristics (parity, women's BMI and current unfulfilled wish to conceive) as well as subjective PCOS-related concerns (women's infertility-related and acne-related concerns) are associated with the sexual and/or relational satisfaction of couples dealing with this chronic disease. Most of these associations were significantly different for PCOS women and their partners.

Firstly, we found that a lower parity tended to be associated with higher levels of sexual and relational satisfaction in both PCOS women and their partners. In contrast, the case-control study by Månsson et al. (2011) concluded that having children or not was not associated with sexual functioning of PCOS women, as measured by the McCoy female sexual rating scale. Additionally, we observed that the presence of a current unfulfilled wish to conceive and a higher level of infertility-related concerns was (significantly) associated with higher levels of relational satisfaction in both PCOS women and their partners. This pattern of results might be explained by the fact that childless couples (i.e. parity = 0) have possibly more time for each other than couples with children (Claxton & Perry-Jenkins, 2008; Lawrence et al., 2008), and that, in case of unwanted childlessness, couples with fertility problems probably have a more stable and satisfying relationship (Månsson et al., 2011). It should be noted, however, that existing evidence on the infertility-satisfaction association is inconsistent. For example, Bringhenti et al. (1997) reported, on the one hand, a significantly higher level of relational satisfaction in women with explained infertility when compared with women without fertility problems, but – on the other hand – no significant differences in relational satisfaction level in women with unexplained infertility when compared with women without fertility problems. Also, Monga et al. (2004) found significantly and non-significantly lower levels of relational satisfaction in infertile versus fertile women and infertile versus fertile men, respectively.

In our study, we observed no association of a current unfulfilled wish to conceive and infertility-related concerns with sexual satisfaction in PCOS women and their partners. This is in line with the Tan et al. (2008) study in which no difference was found in women's satisfaction with their sex life – as measured by using a VAS – between a group of PCOS women with or without a wish to conceive. Similarly, the Iris et al. (2013) study found no significant differences in sexual satisfaction levels between a sample of infertile women and a control group. In contrast Shoji et al. (2014) reported lower sexual satisfaction levels in both partners of infertile couples when compared with both partners of pregnant couples.

Secondly, since PCOS is often accompanied by changes in women's physical appearance (e.g., obesity, hirsutism and acne), one should expect a substantial influence of these symptoms on couple's sexual and relational satisfaction. In line with this expectation we observed – taking into account that only overweight women with PCOS were included in the current study – a trend towards an association between a higher BMI and lower levels of sexual and relational satisfaction in PCOS women. To our knowledge, there is currently no evidence available about the association of BMI with relational satisfaction in a general female population. Our findings on sexual satisfaction are in line with the study by Månsson et al. (2011) in which a trend towards a negative association of an increased BMI with PCOS women's sex life was found. Also in the Yaylali et al. (2010) study a significant negative correlation between weight and the level of sexual satisfaction was found; Brody & Weiss (2013) reported a significant negative correlation between a woman's waist circumference and her level of sexual satisfaction.

A series of studies also documents the opposite pattern. For example, Elsenbruch et al. (2003) and Stovall et al. (2012) concluded that differences in BMI status were not associated with PCOS women's level of sexual satisfaction. Similarly, two studies – performed in a general female sample – found that overweight and obesity (as expressed by BMI) were no risk factors for sexual satisfaction (as measured by the Female Sexual Function Index) (Kadioglu et al., 2010; Yaylali et al., 2010).

Within partners of PCOS women, a higher BMI of PCOS women tended to be associated with higher levels of sexual and relational satisfaction. To our knowledge, there is currently no evidence available from other PCOS studies, nor from non-PCOS studies about this association in a general male sample with which our results could be compared.

We also observed that higher levels of acne-related concern in PCOS women were significantly associated with lower levels of sexual satisfaction within both PCOS women and their partners. The study by Hahn et al. (2005) and by Stovall et al. (2012) reported no significant association of the objective presence of acne with the level of sexual satisfaction and sexual functioning of PCOS women. However, our results reflect the association of PCOS women's concern about the presence of acne with satisfaction, rather than the association of the objective degree of acne with satisfaction.

As the evidence about the association of PCOS characteristics (e.g., BMI, infertility) with sexual/relational satisfaction is inconsistent across samples of infertile and obese women, no conclusions can be drawn about the nature of these associations within those samples. Moreover, since we do not know with certainty whether all women included in these studies were women without PCOS, it is not possible to make a statement about these associations in a non-PCOS population. Taken

together, it is hard to compare our findings with evidence from a non-PCOS population and it is even harder to decide if our findings are unique to a PCOS population.

It should be noted however, that the association of PCOS characteristics with the level of sexual/relational satisfaction might possibly be explained by the influence of confounding factors. For example, depression might influence the association of PCOS with sexual satisfaction, given – on the one hand – the increased depression level in PCOS women compared with age-matched controls (Elsenbruch et al., 2003), and – on the other hand - the significant association of an increased depression level with a decreased sexual satisfaction level in a general sample of sexually active females (Kadioglu et al., 2010). Unfortunately, we were not able to correct our analyses for this confounding factor since we had no detailed information about the presence of depression at the time of recruitment. Nevertheless, given this existing evidence, caution is warranted when interpreting the association of PCOS with the level of sexual satisfaction as reflecting a direct association. This also stresses the importance of adjusting the performed analyses for confounding factors in future research.

Thirdly, we found significantly lower levels of sexual and relational satisfaction in PCOS women when compared with their partners. Thus far, only one study reported on the differential influence of a chronic disease on the satisfaction of both partners in a couple. A study by Van Son-Schoones (1994), investigating the sexual and relational satisfaction (among others) of patients with a chronic kidney disease, observed significantly higher levels of relational satisfaction in patients than their partners ($t = -3.46$, $p < .001$). It should be noted, however, that the study by Van Son-Schoones (1994) included female as well as male patients and the interdependence of both partners in a couple was not taken into account (only half of the patient's partners participated in the study and no dyadic statistical analyses were performed).

To further clarify this finding we compared our results with published normative data on the MMQ (Joseph et al., 2007). In that reference sample, the level of sexual and relational satisfaction seemed to be lower in married women than in married men. Although no significance level is reported by Joseph et al. (2007), this finding is in line with our results. However, we must be aware of the fact that our group of partners include one female partner.

The observed relational satisfaction levels of the PCOS women as well as their partners in our sample were both found to be significantly higher than those in a reference sample (Joseph et al., 2007). These findings suggest that couples participating in our study were generally satisfied about the non-sexual aspect of their intimate relationship; our results therefore await replication within samples of distressed couples dealing with PCOS.

The present study both complements and elaborates upon existing research on PCOS and intimate relationships. An important strength of this study is that dealing with PCOS was analyzed from a dyadic point of view, by including PCOS women and their partners, focusing on multiple aspects of intimate relationships, and by conducting dyadic statistical analyses taking into account the interdependence of both partners in a couple. We should, however, note some limitations of the current study. The most important of these undoubtedly have to do with the small sample used in the present study. A simulation study to explore the power to detect effects of varying size in the current study was performed. Mimicking the data-structure and the observed within-cluster correlation, we found that with 30 couples the study has about 80% power to detect large effects at the 5% significance levels. The power to detect low to medium effects is smaller than 50%. This might be a reason why certain small effects, found in other studies, were not detected in our study. And although the response rate on all questionnaires was quite high, data were partially missing in some couples which resulted in an unbalanced data set. This limitation was dealt with by using linear mixed models. Due to these limitations we suggest that this study should be replicated in a larger sample using the same standardized questionnaires and statistical dyadic analytic techniques in order to enhance the generalizability of the results. Additionally - since this study was performed in a sample of PCOS women who were all overweight - it is also recommended to recruit from a broader population including normal weight PCOS women as well, in order to further clarify the association of overweight with couple's sexual and relational satisfaction and to enhance the generalizability of the results to a general population of couples dealing with PCOS. Finally, causal relationships can't be tested in the present data and the issue of causal ordering remains for future research to resolve.

In conclusion, our results suggest that objective PCOS characteristics as well as subjective PCOS-related concerns are associated with the sexual and relational satisfaction of couples dealing with this chronic disease. The second conclusion that can be drawn from our findings is that there is a differential association of these characteristics with satisfaction levels for PCOS women and their partners. This is an important finding which should be kept in mind during the psychological guidance of couples dealing with PCOS.

Table I. Descriptive statistics of predictors and outcome variables.

Predictors	
Objective characteristics of the polycystic ovary syndrome (PCOS)	
Presence of hirsutism	13/30 (43.3%)
Presence of facial acne	15/31 (48.4%)
Free testosterone (ng/dL)	0.73 (0.77)
Body mass index (kg/m^2)	33.7 (7)
Current unfulfilled wish to conceive	24/31 (77.4%)
Gravidity	
0	21/31 (67.7%)
1	5/31 (16.1%)
≥2	5/31 (16.1%)
Parity	
0	24/31 (77.4%)
1	5/31 (16.1%)
2	2/31 (6.5%)
Irregular menstrual cycle	29/31 (93.5%)
PCOS-related concerns[a]	
Emotions	4.1 (1.4)
Body hair	4.8 (3.7)
Weight	2.7 (1.8)
Infertility problems	3 (1.4)
Menstrual problems	3.3 (1.7)
Acne	1 (6.6)
Outcome variables[b]	
Women with PCOS	
Sexual satisfaction	9.85±8.01
Relational satisfaction	10.59±8.13
Partners	
Sexual satisfaction	7.63±6.05
Relational satisfaction	8.13±5.74

Continuous measurements are summarized as mean±SD if symmetrically distributed, and as median (interquartile range) otherwise.

Nominal measurements are summarized as n(%).

[a]PCOS-related concerns as measured by the PolyCystic Ovary Syndrome Questionnaire and an acne Visual Analogue Scale.

[b]Outcome variables as measured by the sexual and marital satisfaction subscale of the Maudsley Marital Questionnaire.

Table II. Effect of objective characteristics of the polycystic ovary syndrome (PCOS) and PCOS-related concerns on outcome variables in women with PCOS and their partners, and the difference in effect between women with PCOS and their partners.

	Women with PCOS		Partners		Difference		Cohen's f^2
	ß	95% CI	ß	95% CI	ß	95% CI	
Sexual satisfaction							
Objective characteristics of PCOS							
Body mass index (kg/m²)	0.07	(-0.44,0.59)	-0.24	(-0.64,0.16)	0.31*	(0.04,0.59)	0.19
Parity	4.02	(-1.12,9.15)	0.25	(-3.88,4.38)	3.77*	(0.81,6.72)	0.25
PCOS-related concerns[a]							
Acne	1.07*	(0.15,2.00)	1.05**	(0.41,1.69)	0.02	(-0.59,0.65)	0.02
Relational satisfaction							
Objective characteristics of PCOS							
Body mass index (kg/m²)	0.17	(-0.33,0.63)	-0.08	(-0.48,0.31)	0.25*	(0.04,0.47)	0.21
Current unfulfilled wish to conceive	-5.51	(-12.70,1.66)	-1.75	(-7.46,3.96)	-3.76*	(-6.91,-0.63)	0.13
Parity	3.70	(-1.40,8.81)	0.32	(-3.88,4.51)	3.38**	(0.91,5.86)	0.33
PCOS-related concerns[a]							
Infertility problems	2.72*	(0.31,5.13)	1.08	(-0.68,2.84)	1.64*	(0.40,2.88)	0.21

[a]PCOS-related concerns as measured by the PolyCystic Ovary Syndrome Questionnaire and an acne Visual Analogue Scale.

*p < 0.05, **p < 0.01

Veerle De Frène is holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). Petra De Sutter is holder of a fundamental clinical research mandate by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). This research also received financial support by Merck Serono and the Artevelde University College Ghent.

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Chapter 3 A RETROSPECTIVE STUDY OF THE PREGNANCY, DELIVERY AND NEONATAL OUTCOME IN OVERWEIGHT VERSUS NORMAL WEIGHT WOMEN WITH POLYCYSTIC OVARY SYNDROME

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Hum Reprod 2014;29:2333-2338. Epub 2014 Jun 24. Doi: 10.1093/humrep/deu154.

Abstract

Study question: Do overweight women with polycystic ovary syndrome (PCOS) have a higher risk of perinatal complications than normal weight women with PCOS?

Summary answer: Overweight women with PCOS with an ongoing singleton pregnancy have an increased risk of preterm birth as well as an increased risk of giving birth to a baby with a higher birthweight than normal weight women with PCOS.

What is known already: There is evidence that overweight (BMI > 25 kg/m²) has a negative influence on the prevalence of gestational diabetes mellitus and fetal macrosomia in women with PCOS.

Study design, size, duration: We set up a retrospective comparative cohort study of 93 overweight (BMI ≥ 25 kg/m²) and 107 normal weight (BMI < 25 kg/m²) women with PCOS who were scheduled for fertility treatment between January 2000 and December 2009 and achieved a pregnancy as a result of a treatment cycle, or spontaneously before or between treatment cycles.

Participants/materials, setting, methods: All data (patient characteristics, medical information, pregnancy, delivery and neonatal outcome) were retrieved from patient medical files. All pregnancy, delivery and neonatal outcome parameters were adjusted for age and pre-pregnancy smoking behaviour. The neonatal outcome parameters were additionally adjusted for gestational age.

Main results and the role of chance: The median BMI in the overweight and normal weight women was, respectively, 30.8 kg/m² [interquartile quartile range (IQR) 5.8] and 20.9 kg/m² (IQR 2.3) ($P < 0.001$). Baseline characteristics did not differ between groups, except for free testosterone and fasting insulin levels, which were higher, and sex hormone-binding globulin, which was lower, in overweight versus normal weight women (all $P < 0.001$). The time-to-pregnancy was significantly higher in the overweight group ($P = 0.01$). Multivariate analyses of the ongoing singleton pregnancies showed significantly more preterm births in overweight (10/61) versus normal weight (2/71) women [adjusted odds ratio 14.2, 95% confidence interval (CI) 1.8 to 155.6, $P = 0.01$]. The mean birthweight of newborns was significantly higher in overweight (3386±663 g) than in normal weight (3251±528 g) women (adjusted mean difference 259.4, 95% CI 83.4 to 435.4, $P = 0.004$).

Limitations, reason for caution: Our results only represent the pregnancy, delivery and neonatal outcome of ongoing singleton pregnancies. The rather small sample size and observational nature of the study are further limitations.

Wider implications of the findings: Our results suggest the importance of pre-pregnancy weight loss in overweight women with PCOS in order to reduce the risk of adverse perinatal outcomes.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder present in approximately 5-10% of women of reproductive age (Hoeger et al., 2004; Broekmans et al., 2006). It is characterized by the presence of oligo- or amenorrhea, polycystic ovaries, hirsutism, raised LH:FSH ratio, insulin resistance (IR) and compensatory hyperinsulinemia (The Rotterdam ESHRE/ASRM-sponsored consensus workshop group, 2004). IR has an important influence on the development of diabetes type 2 and hypertension (Perciaccante et al., 2006). Hypertension is thought to be associated with androgen excess and a subsequent increased stimulation of sympathetic nerve activity (Perciaccante et al., 2007, Studen et al., 2013). Abdominal overweight and obesity – also important components of PCOS that affect about 30-70% of the PCOS population (Pasquali et al., 2006; Vrbikova & Hainer, 2009) – are associated with IR, increased testosterone production (Pasquali et al., 2006) and increased stimulation of sympathetic nerve activity (Troisi et al., 1991; Scherrer et al., 1994).

Polycystic ovary syndrome in itself has a negative influence on the perinatal outcome for these women. There is evidence that women with PCOS are at increased risk of early pregnancy loss and miscarriages (Wang et al., 2001), which could possibly be caused by pre-pregnancy LH hypersecretion (Regan et al., 1990), hyperandrogenemia (Okon et al., 1998; Kazerooni et al., 2013), overweight (Fedorcsák et al., 2000), hyperinsulinemia and/or thrombophilia (Kazerooni et al., 2013). In women with PCOS, pregnancy is often complicated by pregnancy-induced hypertension, preeclampsia and gestational diabetes mellitus (GDM) and also the risk for a preterm delivery or a delivery by Caesarean section is raised (Boomsma et al., 2006; Altieri et al., 2010; Kjerulff et al., 2011; Qin et al., 2013). The newborn babies stay more frequently in a neonatal intensive care unit and perinatal mortality also occurs more frequently (Boomsma et al., 2006; Qin et al., 2013). Since it has been proven that pre-pregnancy maternal overweight and obesity have a negative influence on the perinatal outcome (Bogaerts et al., 2012; Blomberg , 2013; Cnattinguis et al., 2013; Crane et al., 2013), existing retrospective studies comparing the perinatal outcome in women with PCOS versus women without PCOS have matched the samples for BMI or have adjusted the analyses for BMI. As such, Mikola et al. (2001) and Turhan et al. (2003), looking into the pregnancy, delivery and neonatal outcome in women with PCOS, concluded that pre-pregnancy overweight (BMI > 25 kg/m²) is an important predictor of GDM. A study by Han et al. (2011) of Asian women looked into the influence of overweight (BMI > 25 kg/m²) on the pregnancy outcome in women with PCOS, using a case-control design of overweight versus non-overweight women, and showed that the prevalence of GDM and fetal macrosomia was significantly higher in overweight versus normal weight women with PCOS.

Since these studies are rather scarce and, to date, only performed in an Asian population, we performed a retrospective cohort study comparing the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with PCOS using multivariate analyses.

Materials and methods

Design

A retrospective comparative cohort study was conducted at the Department of Reproductive Medicine of the Ghent University Hospital, Ghent, Belgium. The study population included 93 overweight and 107 normal weight women with PCOS between the age of 18 and 43 years who were pregnant (i.e. positive hCG at 4 weeks after the start of the last menstrual cycle) as a result of a treatment cycle, or spontaneously before the start or between treatment cycles. All study participants were scheduled for a treatment at the fertility center between January 2000 and December 2009. There was no upper BMI limit impeding women from undergoing a fertility treatment. Only the first pregnancy was taken into account. PCOS was diagnosed using the diagnostic criteria of the Rotterdam consensus 2003 (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Women scheduled for a fertility treatment between 2000 and 2003 were reclassified as PCOS patients according to the Rotterdam criteria. Those women who fulfilled these criteria, were included in the study. Women with pathologies (such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors) which present or imitate the same characteristics as PCOS were excluded. All data (patient characteristics, medical information, pregnancy, delivery and neonatal outcome) were retrieved from patient medical files. If delivery took place in another hospital, data on pregnancy, delivery and neonatal outcome were obtained through the treating gynecologist of that hospital.

Measures

A polycystic ovarian morphology (PCOM) was diagnosed by means of transvaginal ultrasound showing the presence of ≥ 12 follicles with a diameter of 2-9 mm and/or an increased ovarian volume of > 10 cm^3 (using the formula 4/3 π abc). Participants were described as having an irregular menstrual cycle if they had oligomenorrhea (i.e. no menstrual bleeding for > 35 days) or amenorrhea (i.e. no menstrual bleeding for > 6 months). Hirsutism was diagnosed by the presence of a self-reported mild or severe degree of visible hair growth, and hyperandrogenemia was diagnosed by the presence of a free testosterone (fT) level > 0.50 ng/dL. An LH:FSH ratio > 2 was classified as abnormal. Basal hormone levels [i.e. LH, FSH, testosterone, fT and sex hormone-binding globulin (SHBG)] were determined at day 2 or 3 of a spontaneous or induced menstrual cycle and – in case of a hormonal treatment – prior to that therapy. Fasting insulin and glucose levels were also assessed. Biochemical analyses were performed at the laboratory of the Ghent University Hospital using the electrochemiluminiscence immunoassay technique (Modular, Roche Diagnostics, Mannheim, Germany). Pre-pregnancy overweight was defined as a BMI of ≥ 25 kg/m^2 (WHO, 2010). All normal weight women had a pre-pregnancy BMI below 25 kg/m^2. The participant's body weight and height were measured before the

fertility treatment by using an electronic personal scale and a stadiometer respectively in order to calculate their BMI. The pre-pregnancy smoking behaviour was evaluated as present (i.e. at least one cigarette a day) or not (yes/no answer). It could not be determined whether the women who were known to be smokers, continued smoking or quitted during pregnancy.

To study the pregnancy outcome, data on the presence of miscarriage, multiple pregnancy, hypertension during pregnancy, preeclampsia and diabetes during pregnancy were collected. A miscarriage was classified as a first or second trimester miscarriage when loss of the fetus occurred in the first 13 weeks of pregnancy or between 14 and 25 weeks of pregnancy, respectively. Since we had no data on blood pressure and the diabetic status of each woman before pregnancy, we used the term hypertension during pregnancy (HDP) and diabetes during pregnancy (DDP) instead of pregnancy-induced hypertension and GDM, respectively. Preeclampsia was diagnosed by the presence of hypertension during pregnancy (i.e. a blood pressure > 140/90 mmHg) and proteinuria > 300 mg/day. According to the guidelines of the American Diabetes Association, DDP was diagnosed at approximately 24 weeks of gestation using the oral glucose tolerance test (American Diabetes Association, 2014).

To study the delivery outcome, data on gestational age and mode of delivery were gathered. A gestational age of < 32 weeks (starting from the first day of the last menstrual period) and between 32 and 37 weeks was classified as a very preterm birth and a preterm birth, respectively. The mode of delivery was observed as a variable with two categories, i.e. Caesarean section or vaginal delivery. The use of an epidural analgesia during a vaginal delivery was also registered.

Regarding the neonatal outcome, the birthweight was expressed in grams and a distinction was made between a low and a very low birthweight, representing a birthweight between 1500 and 2500 grams or < 1500 grams, respectively. Macrosomia was diagnosed if birthweight was more than 4000 grams. If children had adaptation problems, admission to a neonatal (intensive) care unit was also registered.

Ethical approval

This retrospective study was authorized by the Ethics Committee of the Ghent University Hospital. Informed consent from patients was not obtained but patient information was anonymized and de-identified prior to analysis.

Statistical analyses

Statistical analyses were performed using SPSS version 21.0. Independent samples t-tests, Mann-Whitney U, Chi-square and Fisher Exact tests were used where appropriate and were performed at the 5% significance level. The normal distribution of continuous variables was graphically inspected using

QQ-plots. Univariate odds ratios (OR) and confidence intervals (CI) were based on small sample adjustments where needed (Jewell, 2003). Given the observational nature of the study, multiple linear and logistic regression was performed to adjust for confounding factors in all outcome analyses. In particular, the analyses of the miscarriage rate, the ongoing multiple pregnancy rate and the ongoing singleton pregnancy, delivery and neonatal outcomes were adjusted for age and pre-pregnancy smoking behaviour, since research has proven their negative influence on the perinatal outcome (Lowe et al., 1998; Delbaere et al., 2007; Cnattingius et al., 2013). The neonatal outcome parameters were additionally adjusted for gestational age (Land, 2006). Effects of overweight on neonatal outcome parameters must therefore be interpreted as reflecting the effects that cannot be explained by intermediate effects via gestational age. Adjusted odds ratios (AOR) and 95% CI were calculated for all outcome parameters and residual analyses confirmed the adequacy of the models.

Since multiple pregnancies have an important negative influence on perinatal outcome (The ESHRE Capri Workshop Group, 2000), we focused our analyses on the pregnancy, delivery and neonatal outcome of ongoing singleton pregnancies.

Results

Baseline characteristics

Our sample consisted of 200 pregnant women with PCOS of whom 119/200 (59.5%) had full-blown PCOS, 31/200 (15.5%) suffered from oligo- or anovulation and hyperandrogenism, 39/200 (19.5%) had PCOM and oligo- or anovulation, and 11/200 (5.5%) suffered from hyperandrogenism and PCOM.

The baseline characteristics of the overweight and normal weight group are summarized in Table I. The difference in median BMI between groups was 9.9 kg/m² ($P < 0.001$). The LH:FSH ratio was less than 2 in both groups and this ratio was not significantly different between the overweight and normal weight women. There was a significant difference in the fT, SHBG and fasting insulin levels, as well as in the time-to-pregnancy. The fT level was significantly higher in the overweight group and the SHBG level was significantly lower in the overweight group. The fasting insulin level was only elevated in the overweight group.

Perinatal outcome

In the overweight and normal weight group there were 22/93 (23.7%) and 25/107 (23.4%) miscarriages, resulting in 71 and 82 ongoing pregnancies, respectively (AOR 1, 95% CI 0.5 to 2.0, $P = 0.9$). All miscarriages, except one in the overweight group, were first trimester miscarriages. In both groups there were two ectopic pregnancies. The prevalence of ongoing multiple pregnancies was 8/69 (11.6%) in the overweight group and 9/80 (11.3%) in the normal weight group (AOR 1.1, 95% CI 0.4 to 3.1, $P = 0.9$). In each group one triplet pregnancy occurred.

Data on the pregnancy, delivery and neonatal outcome of ongoing singleton pregnancies in overweight and normal weight women are reported in table II. No significant differences were detected in the prevalence of HDP and preeclampsia between the overweight and normal weight group. In one normal weight woman preeclampsia evolved to eclampsia. Despite the significant difference in fasting insulin levels between the two groups, there was no significant difference in prevalence of DDP. The age of the study participant was a significant predictor of the prevalence of DDP ($P = 0.03$), namely the older the participant, the more likely she was to develop DDP.

There was marginal evidence of a difference in gestational age between overweight and normal weight women (adjusted mean difference -4.8, 95% CI -9.7 to 0.1). The prevalence of preterm birth was significantly higher in overweight versus normal weight women. In the overweight group, one very preterm birth (25 weeks of pregnancy) occurred. With regard to the mode of delivery, there was marginal evidence of a difference in the prevalence of Caesarean sections versus vaginal deliveries

between groups. Reasons for delivery through Caesarean section were fetal distress, a malpresentation, a narrowed pelvis and a prolonged labour. In the overweight group one caesarean section was performed under general anesthesia. An epidural analgesia was used otherwise.

There was a significantly higher birthweight in babies of overweight versus normal weight women, even after additional adjustment for gestational age (adjusted mean difference 259.4, 95% CI 83.4 to 435.4). We found no evidence of a higher prevalence of macrosomia in overweight versus normal weight women. In the overweight group, there was one newborn with a very low birthweight of 700 grams due to a very preterm birth.

Since the study included one overweight woman with a very preterm birth (gestational age of 25 weeks) of a very low birthweight baby (700 grams), a sensitivity analysis was performed by removing this case from the analysis of the pregnancy, delivery and neonatal outcome in ongoing singleton pregnancies. The exclusion of this study participant had no influence on the results.

We also performed a scenario analysis using the cut-off of 30 kg/m² instead of 25 kg/m² to evaluate the influence of obesity on the perinatal outcome in women with PCOS. The results showed marginal evidence of a higher prevalence of Caesarean sections versus vaginal deliveries in the obese group (AOR 2.5, 95% CI 1.1 to 5.9, P = 0.04) and of a difference in preterm birth between both groups (AOR 3.5, 95% CI 1 to 12.4, P = 0.05). All other results were similar to those of the original analysis.

Discussion

The results of our study support the hypothesis that pre-pregnancy overweight in women with PCOS has, in addition to the negative effect of the syndrome in itself, a negative influence on the prevalence of preterm birth and the birthweight of singletons. Marginal evidence is found of a shorter gestational age and a higher prevalence of Caesarean sections in ongoing singleton pregnancies of overweight versus normal weight women. No significant difference in miscarriage rate was observed between overweight and normal weight women.

Concerning the miscarriage rate, our results are the opposite of those in the retrospective cohort study by Fedorcsák et al. (2000) investigating the influence of overweight (BMI ≥ 25 kg/m²) on the prevalence of early pregnancy loss in a sample of infertile women who received IVF or ICSI. They conclude that overweight was an independent risk factor for early pregnancy loss before 12 weeks of gestation (Fedorcsák et al., 2000). A cohort study by Wang et al. (2001) found evidence that a pre-pregnancy BMI of 30 to 34.9 kg/m² has a significant negative and independent influence (AOR 1.79, 95% CI 1.16 to 2.75) on the prevalence of pregnancy loss before 20 weeks of gestation in women with PCOS.

Our findings suggest that pre-pregnancy overweight has a negative influence on the prevalence of preterm birth. A similar result was found by Cnattingius et al. (2013), studying the association between maternal obesity and the risk of preterm delivery in Swedish women using a retrospective design. These authors observed that obesity (BMI ≥ 30 kg/m² to ≥ 40 kg/m²) had a significant influence on the prevalence of preterm birth (gestational age < 37 weeks) and this negative influence was highest in extremely preterm births (gestational age of 22 to 27 weeks). We cannot confirm this last statement because there was only one very preterm birth (gestational age of 25 weeks) in the overweight group, which was due to blood loss and preterm contractions. In contrast, the case-control study by Han et al. (2011) found no significant influence of overweight (BMI > 25 kg/m²) in women with PCOS on the prevalence of preterm birth. It has to be mentioned that these analyses were not adjusted for other important covariates.

In line with the conclusions of Han et al. (2011), our results showed that the birthweight of the newborn was significantly higher in overweight women in comparison to normal weight women. In contrast to Han et al. (2011), this result was only significant after adjustment for gestational age among others, which emerged as a significant predictor of birthweight. Our results thus express the direct effect of pre-pregnancy overweight on neonatal outcome, other than via gestational age, rather than the overall effect reported by Han et al. (2011).

Our findings do not confirm the existing evidence that overweight has an influence on the prevalence of macrosomia and GDM (Mikola et al., 2001; Turhan et al., 2003; Han et al., 2011). Although we did not find a significant difference in DDP, none of the normal weight women had DDP in comparison to 8.2% in the overweight group.

Although there is evidence that a treatment with IVF/ICSI has a negative influence on the prevalence of preterm birth in singleton pregnancies (Maman et al., 1998; Dhont et al., 1999), we could not confirm this since the treatment-to-pregnancy (i.e. the last treatment that has led to pregnancy) was not significantly associated with outcome in any of the analyses performed.

While we have adjusted for the confounding factors pre-pregnancy smoking behaviour and maternal age, a limitation of our study is that the comparison of overweight versus normal weight women with PCOS may be confounded by other, possibly unmeasured, factors. Caution is therefore warranted when interpreting all results as reflecting the influence of overweight. A further limitation is that our results for pregnancy, delivery and neonatal outcome can only be generalized to singleton ongoing pregnancies and that our analysis may also be vulnerable to selection bias due to the restriction to pregnant women who had experienced fertility problems. This restriction, while difficult to avoid, may induce bias as a result of the fact that pregnancy and fertility problems may themselves be influenced by overweight (Rosenbaum, 1984). For this reason the results may not be generalizable to the general PCOS community. Finally, because of the rather small sample size of ongoing singleton pregnancies (n=132) and the resulting lack of power, non-significance of certain associations should not necessarily be interpreted as indicating the lack of association. A larger confirmatory study is therefore indicated, as well as a similar study looking into the influence of pre-pregnancy overweight in women with PCOS on the pregnancy, delivery and neonatal outcome in multiple pregnancies.

In our study, we focused on the influence of pre-pregnancy overweight rather than the gestational weight gain on perinatal outcome. In women without PCOS, gestational weight gain is also found to be an important predictor of perinatal complications (Bogaerts et al., 2012) and therefore an important factor to keep in mind during the medical supervision of pregnancy, delivery and postpartum. It would be interesting in the future to perform a prospective follow-up study looking into the difference in influence of pre-pregnancy BMI versus gestational weight gain on perinatal outcome in women with PCOS.

We conclude that pre-pregnancy overweight in women with PCOS has, in addition to the influence of the syndrome in itself, an important negative influence on the prevalence of preterm birth and the birthweight of the newborn singleton. Therefore we suggest the importance of pre-pregnancy weight loss in overweight women with PCOS in order to reduce the risk of adverse perinatal outcomes.

Table I. Baseline characteristics of overweight versus normal weight women with polycystic ovary syndrome.

Characteristics	**Overweight** (n = 93)	**Normal weight** (n = 107)	***P***
Age (years)	29±4.2	28.4±3.1	0.3
BMI (kg/m²)	30.8 (27.7-33.5)	20.9 (20-22.3)	<0.001
Smoking	22/91 (24.2%)	18/101 (17.8%)	0.3
Primigravida	70/93 (75.3%)	87/107 (81.3%)	0.3
PCOM[a]	73/87 (83.9%)	96/105 (91.4%)	0.1
Irregular menstrual cycle	86/93 (92.5%)	103/107 (96.3%)	0.4
Hirsutism	38/64 (59.4%)	46/77 (59.7%)	1
LH:FSH ratio	1.5 (0.9-2.2)	1.6 (1-2.5)	0.4
Testosterone (ng/dL)	48.6 (38.5-61.9)	46.9 (34-62.6)	0.3
Free testosterone (ng/dL)	0.8 (0.6-1.1)	0.5 (0.4-0.8)	<0.001
SHBG[b] (nmol/L)	33.6 (21.9-50.6)	62.1 (46.9-82.9)	<0.001
Fasting insulin (µU/mL)	14 (7.8-22.5)	7.3 (4.7-10)	<0.001
Treatment-to-pregnancy[c]			0.4
Spontaneous pregnancy	11/93 (11.8%)	12/107 (11.2%)	
Timed coitus	12/93 (12.9%)	21/107 (19.6%)	
Intrauterine insemination	36/93 (38.7%)	39/107 (36.4%)	
IVF/ICSI	34/93 (36.6%)	35/107 (32.7%)	
Time-to-pregnancy[d] (months)	32 (20.3-49)	26 (17-36.5)	0.01

Continuous measurements are summarized as mean±SD if symmetrically distributed, and as median (1st quartile-3rd quartile) otherwise.
Nominal measurements are summarized as n(%).
[a]PCOM = polycystic ovarian morphology.
[b]SHBG = sex hormone-binding globulin.
[c]Treatment-to-pregnancy = the last treatment that has led to pregnancy.
[d]Time-to-pregnancy = the duration of the desire to have children.

Table II. Pregnancy, delivery and neonatal outcome in singleton ongoing pregnancies of overweight versus normal weight women with PCOS.

	Overweight (n=61)	**Normal weight** (n=71)	**Crude OR (95% CI)**	***P***	**Adjusted OR (95% CI) - JUIST**	***P***
Pregnancy outcome						
Hypertension during pregnancy	3/61 (4.9%)	4/71 (5.6%)	0.9 [0.1-5.4]	1	0.9 [0.2-4.2]	0.9
Pre-eclampsia	4/61 (6.6%)	4/71 (5.6%)	1.2 [0.2-6.6]	1	0.9 [0.2-4.2]	0.9
Diabetes during pregnancy	5/61 (8.2%)	0/71	/	0.02	/	1
Delivery outcome						
Gestational age (in days)	276 (265.5-283)	277 (273-282)	/	0.4	/	0.06
Preterm birth (< 37 weeks)	10/61 (16.4%)	2/71 (2.8%)	6.7 [1.3-65.3]	0.01	14.2 [1.8-155.6]	0.01
Caesarean section	20/61 (32.8%)	14/71 (19.7%)	2 [0.9-4.4]	0.1	2.2 [1-5.1]	0.06
Neonatal outcome						
Birthweight (in grams)	3386.1±663.3	3251.3±528	/	0.2	/	0.004
Low birthweight (< 2500 g)	3/61 (4.9%)	3/71 (4.2%)	1.2 [0.2-9]	1	0.2 [0-2.8]	0.3
Macrosomia (> 4000 g)	6/61 (9.8%)	6/71 (8.5%)	1.2 [0.4-3.9]	1	1.3 [0.4-4.4]	0.7
Stay in neonatal (intensive) care unit	11/61 (18%)	9/71 (12.7%)	1.5 [0.6-3.9]	0.5	0.7 [0.2-2.3]	0.5

Continuous measurements are summarized as mean±SD if symmetrically distributed, and as median (IQR) otherwise.

Nominal measurements are summarized as n(%).

Pregnancy and delivery outcomes are adjusted for age and smoking behaviour

Neonatal outcomes are adjusted for age, smoking behaviour and gestational age

Veerle De Frène is holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). Petra De Sutter is holder of a fundamental clinical research mandate by the Flemish Foundation for Scientific Research (FWO-Vlaanderen).

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Chapter 4 QUALITY OF LIFE AND BODY MASS INDEX IN OVERWEIGHT ADULT WOMEN WITH POLYCYSTIC OVARY SYNDROME DURING A LIFESTYLE MODIFICATION PROGRAM

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J Obstet Gynecol Neonatal Nurs 2015. Epub ahead of print 2015 Aug 18. Doi: 10.1111/1552-6909.12739.

Abstract

Objective: This study was performed to evaluate changes in body mass index (BMI) and health-related quality of life (HRQoL), including an acne parameter, of overweight adult women with polycystic ovary syndrome (PCOS) during a lifestyle modification program.

Design: Prospective longitudinal within-patient study.

Setting: Department of Reproductive Medicine of the Ghent University Hospital (Belgium).

Participants: Thirty-three overweight (BMI ≥ 25 kg/m²) women with PCOS between the age of 18 and 43 years.

Methods: Participants followed a 24-week lifestyle modification program, consisting of a diet, exercise, and psychological subprogram. BMI was assessed at week 0, 8, 16 and 24 of the program. The HRQoL was measured at week 0, 12 and 24 of the program using the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) and a Visual Analogue Scale (VAS) evaluating the influence of acne on HRQoL.

Results: Over a 24-week period no significant decrease in BMI occurred (mean difference = 1.71, 95% CI [-1.38, 4.81]. During that period, there was a significant positive evolution of the total PCOSQ score ($F(2,37.5) = 23.7$), the emotions ($F(2,37.9) = 4.2$), weight ($F(2,42.1) = 24.8$), body hair ($F(2,35.6) = 3.3$), and infertility problems domain scores ($F(2,43.1) = 15.64$) of the PCOSQ, as well as of the acne VAS score ($F(2, 29.3) = 4.2$). These effects primarily occurred during the first 12 weeks.

Conclusion: In spite of no significant changes in BMI, the HRQoL of overweight adult women with PCOS significantly improved during a 24-week lifestyle modification program.

Introduction

The polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age worldwide (Broekmans et al., 2006). Overweight and obesity are present in 30-70% of women with PCOS and worsen the PCOS symptom profile. More specifically, the prevalence of hirsutism, menstrual cycle irregularities, anovulation, and infertility is higher in overweight and obese women with PCOS when compared with normal weight women with PCOS (Gambineri, Pelusi, Vicennati, Pagotto, & Pasquali, 2002; Vrbikova & Hainer, 2009). Overweight in women with PCOS also has in itself as well as via the above mentioned PCOS characteristics, a negative influence on women's health-related quality of life (HRQoL) (Jones, Hall, Balen, & Ledger, 2008). Weight loss is therefore a crucial first step in the treatment of PCOS in overweight women. A weight loss of 5-10% through lifestyle modification improves menstrual regularity, restores ovulation, and consequently increases the chance to become pregnant (Hoeger, 2006; Hoeger et al., 2004; Huber-Buchholz, Carey, & Norman, 1999; Norman, Davies, Lord, & Moran, 2002; Tang et al., 2006; Thessaloniki ESHRE/ASRM-Sponsored Consensus Workshop Group, 2008). There is also increasing evidence that lifestyle modification has a positive effect on women's HRQoL. A 24-week randomized controlled trial in obese adolescent women with PCOS, revealed that a treatment of lifestyle modification and oral contraceptives, with or without metformin, had a positive effect on HRQoL (Harris-Glocker, Davidson, Kochman, Guzick, & Hoeger, 2010). Similarly, a 20-week lifestyle modification treatment, consisting of diet with or without exercise, had a positive impact on HRQoL in overweight and obese adult women with PCOS (Thomson et al., 2010).

Evidence about the isolated effect of exercise and diet interventions on psychological well-being in women with PCOS is limited. Liao et al. (2008) found that a self-directed walking program significantly reduced the level of body image distress in overweight and obese women with PCOS. Galletly et al. (2007) reported a lower depression rate and higher level of self-esteem after a high-protein diet when compared with a low-protein diet. To date, there is no evidence about the isolated effect of psychological interventions on the psychological well-being of women with PCOS.

Notwithstanding the promising results of the Harris-Glocker et al. (2010) and Thomson et al. (2010) studies, their findings are limited in several respects. Firstly, only one of these studies focused on the effect of lifestyle modification in adult women with PCOS. Secondly, that study did not include an individual psychological subprogram in the treatment of overweight and obesity that seems to be important in weight loss programs in order to obtain a maximum effect (Shaw, O'Rourke, Del Mar, & Kenardy, 2005). Finally, neither of the two studies included an evaluation of the influence of acne on women's HRQoL although this was reported as a limitation when studying HRQoL in women with PCOS (Jones et al., 2004). Since HRQoL is an important marker from the patient's perspective for the efficacy

of a treatment (Cronin et al., 1998), additional research on this topic is needed. Accordingly, we studied changes in body mass index (BMI) and HRQoL, including an acne parameter, of overweight adult women with PCOS during a 24-week lifestyle modification program, consisting of a diet, exercise and psychological subprogram. Therefore, we hypothesized that (a) the BMI decreases and (b) the level of HRQoL increases during the 24-week LMP in overweight women with PCOS.

Methods

Ethics approval

This study has been reviewed and approved by the Ethics Committee of the Ghent University Hospital. Participants gave their written informed consent for participation in the study.

Design, setting and participants

We set up a prospective longitudinal within-patient study at the Department of Reproductive Medicine of the Ghent University Hospital (Belgium). Participants were recruited by the treating gynecologist during consultation from April 2007 till April 2009 using convenience sampling. Data collection ended in October 2009. Inclusion criteria stipulated that women had to be (a) diagnosed with PCOS, (b) overweight (BMI ≥ 25 kg/m²), and (c) between the age of 18 and 43 years. PCOS was diagnosed by a gynecologist using the Rotterdam criteria (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004).

Demographic and clinical characteristics

Data on demographic and clinical characteristics were gathered by the program coordinator at the start of the LMP. Age and highest level of education (i.e., secondary or higher education) of each participant were collected during interview. Hirsutism was diagnosed by using the modified Ferriman-Gallwey (mFG) scale. The program coordinator classified the participants as hirsute when they had a mFG score ≥ 8 (Ferriman & Gallwey, 1996; Yildiz, Bolour, Woods, Moore, & Azziz, 2010). The presence of facial acne was evaluated by questioning the participants if they were bothered by facial acne or not. Hyperandrogenemia was diagnosed in the presence of a free testosterone level > 0.50 ng/dL, which was determined at day 2 or 3 of a spontaneous or induced menstrual cycle. Menstrual cycle irregularity was diagnosed when participants reported no menstrual bleeding for > 35 days (i.e., oligomenorrhea) or for > 6 months (i.e., amenorrhea). Gravidity and parity were observed as nominal variables answering the questions “Have you already been pregnant at least once?” and “Have you already given birth at least once?”, respectively. Participants were also asked whether they had a current unfulfilled wish to conceive or not.

Intervention

All participants followed a 24-week lifestyle modification program (LMP) consisting of a diet, exercise and psychological subprogram. Throughout the duration of the LMP, consultations with a team of professionals were planned at fixed moments in time (Table 1). Consultations with the dietician and the physiotherapist were planned at week 0, 4, 8, 16, and 24 of the LMP. The frequency of the diet and exercise intervention was higher during the first part of the LMP in order to make sure that the

participants adapted well to the new dietary and exercise pattern. Afterwards it was assumed that participants were informed well enough to execute the diet and exercise advice on their own for a longer period of time (Mertens, Vlayen, & Muls, 2003). The first consultation with the dietician and the physiotherapist lasted one hour and the following consultations lasted 30 minutes. Consultations with the psychologist were planned at week 0, 12, and 24 of the LMP. In addition to these fixed psychological consultations, an extra moment of psychological counseling was possible upon the demand of the participant at week 4, 8, 16, and 20 of the LMP. During these psychological counseling sessions fertility problems were mostly discussed. Each psychological consultation lasted one hour.

All participants were coached individually and interventions were tailored to each participant's degree of overweight and individual abilities. Upon participant's wish, an important other (e.g., partner, mother) was allowed to attend all consultations. A schematic overview with the key content components for the diet, exercise and psychological subprogram are reported in Table 2. Next, the content for each subprogram is described in detail.

The diet subprogram was led by a dietician and consisted of a mild energy restricting diet (i.e., calorie restriction of 450 to 850 Kcal/day) in order to achieve an average weight loss of 0.5 kg (i.e., 1.1 lbs) per week. At the start of the program, participants were taught some general dietary principles: (1) following a daily dietary pattern of three principal meals alternated with three snacks; (2) consuming healthy food; (3) a balanced meal composition; and (4) consuming at least 1.5 L of calorie free drinks per day (e.g., water, light drinks). Additionally, all participants received personalized advice that was based on written information about a participant's eating habit received via the use of a diet diary, on the one hand, and based on oral information about a participant's taste preferences received during consultation, on the other hand. The diet diary was a very detailed registration of the participant's consumed foods and drinks during three days during the week (i.e., two week days and one weekend day) (Becker-Woudstra, van Kuijeren, & Linden-Wouters, 2003). The personalized advice was supported by a list of foods and drinks that should be chosen and those that should be limited in use.

The exercise subprogram was led by a physiotherapist and was focused on raising the level of physical activity during daily life. The participant's level of physical activity was monitored during the entire duration of the LMP by counting the number of steps per day by means of a pedometer (i.e., the Yamax Digiwalker SW-200) (Crouter, Schneider, Karabulut, & Basset, 2003). This tool was used since it has been shown to be a motivational aid for increasing an individual's physical activity level (Merom et al., 2007). During the first week of the LMP, every participant was asked to provide her total number of steps per day while performing usual daily activities in order to determine her baseline activity level. Starting from week two of the LMP, participants started to follow up the advice of the physiotherapist.

This advice consisted of suggestions on how to raise physical activity during daily life at home (e.g., going to the store on foot or with the bike instead of by car, taking the stairs instead of the elevator) and at work (e.g., taking a walk during the break in case of a sedentary job, going to your colleague instead of making a call to discuss something with her/him). Further, the physiotherapist provided concrete advice about how to practice a chosen sport.

The psychological subprogram was led by a psychologist and encompassed individual cognitive behavioral therapy (CBT) (Shaw et al., 2005). Behavioral and cognitive strategies were offered for PCOS related problems (such as body image and eating behavior) and for problems associated with the LMP itself (such as motivation and stress). CBT was focused on defining and changing negative thoughts, like "Life is too busy to go to the gym" or "I can't live without my sweets". Other techniques consisted of problem solving strategies ("If I start eating candy, I can't stop"), goal setting ("I will eat healthy this week") and increasing social support ("My partner buys a lot of chocolate every week").

The program coordinator had personal or telephonic contact with each participant every two weeks to evaluate and solve problems (e.g., concerns about the progression of the LMP, rescheduling appointments) experienced by them during the LMP.

Outcome measures

BMI

The participant's BMI was measured at week 0, 8, 16, and 24 of the LMP by the dietician. In order to calculate the BMI (in kg/m²) participant's body weight (in kg) and height (in m) were measured by using an electronic personal scale and a stadiometer.

HRQoL

The HRQoL was assessed using the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) at week 0, 12, and 24 of the LMP (Cronin et al., 1998; Guyatt, Weaver, Cronin, Dooley, & Azziz, 2004). Upon the start of the LMP, the psychologist gave basic instructions to the participants on how to fill out the PCOSQ. The PCOSQ is a disease-specific questionnaire that evaluates women's subjective perception of the effect of specific PCOS characteristics on their quality of life. The 26-item PCOSQ consists of five domains: emotions, body hair, weight, infertility problems and menstrual problems. Each item was scored on a 7-point Likert scale (1= *high concern*, 7= *no concern*) (Cronin et al., 1998). The mean score of all domain-specific items and the mean score of the five domain scores generated the score of each PCOSQ domain and the total PCOSQ score, respectively, with higher scores indicating qualitatively higher levels of HRQoL. We retained the original time frame of two weeks for the HRQoL measurement

at 12 and 24 weeks of the LMP (Cronin et al., 1998). To measure the baseline HRQoL at the start of the LMP, we used a time frame of six months. In this study, the separate PCOSQ domain scores and the total PCOSQ score showed good reliability (Cronbach's alpha's ranging from .73 to .95), with the exception of the menstrual problems domain scores at the start of the LMP (Cronbach's alpha .57) (Table 3). The construct, content, discriminant, and longitudinal validity were confirmed by prior research (Coffey, Bano, & Mason, 2006; Guyatt et al., 2004; McCook, Reame, & Tatcher, 2005). Jones et al. (2004) assessed the face validity by interviewing 12 adult women with PCOS. About 25% raised their concern about the lack of questions that addressed the influence of acne on HRQoL. Given the fact that acne is a common symptom of PCOS, this result suggested that the face validity could be improved by the addition of an acne domain to the questionnaire. Therefore, we additionally assessed to what extent the facial acne influenced participant's HRQoL by means of a Visual Analogue Scale (VAS) (0= *no influence*, 10= *great influence*). Contrary to the PCOSQ scores, lower VAS scores reflect a better quality of life.

Statistical methods

In order to test the hypothesis that (a) there is a decrease in BMI and (b) an increase in the level of HRQoL during the 24-week LMP, we analysed the evolution of the BMI, the total PCOSQ score, the five PCOSQ domain scores and the acne VAS score, separately.

Linear mixed models

Linear mixed model (LMM) analyses were used to account for correlated measures of the same individual at different points in time. In LMM analyses - under the assumption that missing data are random - all observations, available for a given participant, are used in the analysis (West, Welch, & Galecki, 2006), meaning that a participant with missing observations is not completely removed from the dataset (i.e., listwise deletion).

To find the best fitting model, we used a top-down model building strategy (see West et al., 2006 for more details). The covariates time (weeks in program), age and education level, as well as a model-specific set of time-invariant covariates, all assessed at the start of the LMP, were included in each model. The time-invariant covariates were the BMI at the start of the program for the weight domain; the mFG score and the free testosterone level for the body hair domain; the presence of a current unfulfilled wish to conceive and the parity for the infertility problems domain; the presence of menstrual irregularity for the menstrual problems domain; and the presence of facial acne for the acne VAS. All continuous covariates were centred. Initially, each of the covariates' interactions with the time variable was entered in the model. Non-significant interactions were removed following a backward procedure. To provide an absolute value for the goodness-of-fit, marginal and conditional R^2 values

were calculated for each model following the procedures described in Nakagawa & Schielzeth (2013). Residual analyses did not reveal severe violations of the assumptions underlying the linear model. F values reported for the LMM analyses are Type III Wald F tests with Kenward-Roger degrees of freedom.

Planned contrasts

Once the best fitting model was found, appropriate planned contrasts between time points were examined in order to scrutinize temporal effects. The *p* values for each contrast were Bonferroni corrected to account for the familywise error rate due to multiple testing in each domain.

Software

The LMM analyses were performed using the lme4 package version 1.0-4 in R version 3.0.2 (Bates, Maechler, Bolker, & Walker, 2013; R Core Team, 2013). All other statistical analyses were performed using SPSS version 21.0. The statistical significance level was set at $\alpha < .05$.

Results

Thirty-three study participants met the inclusion criteria. Thirty-one of them effectively participated in the study and started the LMP. Sample characteristics at the start of the LMP are reported in Table 4. In total, 8/31 (25.8%) of the included women dropped out, of which six dropped out before 12 weeks and another two after 12 weeks of the LMP. After 16 weeks, no dropouts occurred. The dropout group did not differ from the remaining group in terms of demographic and clinical characteristics (all *p* values ≥ .05). The response rate on the PCOSQ at week 0, 12, and 24 of the LMP was 30/31 (96.8%), 22/25 (88%) and 22/23 (95.7%), respectively. Seven participants used one or more extra sessions of psychological counseling.

During the LMP, 13/31 (42%) participants received a fertility treatment. Three participants in the non-dropout group became pregnant during the LMP. There was no significant difference ($p \geq .05$) in all outcome parameters between the pregnant and non-pregnant participants at the different moments in time.

Baseline PCOSQ and VAS scores

At baseline, weight was of highest concern with a median domain score of 2.6 [Interquartile range (IQR) = 1.85] followed by infertility problems (*Mdn* = 3, IQR = 1.38), menstrual problems (*Mdn* = 3.38, IQR = 1.63), emotions (*Mdn* = 4.13, IQR = 1.31) and body hair domains (*Mdn* = 4.8, IQR = 3.7). Although body hair was of least concern, the median body hair domain score in hirsute women was 3.1 (IQR = 2.5) when compared with 6.6 (IQR = 2.6) in non-hirsute women ($p = .001$). The infertility problems domain correlated significantly and positively with parity ($r_s = .441$, $p = .02$). The score for this domain was also significantly different between participants with (*Mdn* = 2.75, IQR = 1) and without a current unfulfilled wish to conceive (*Mdn* = 4.25, IQR = 2, $p < .001$), hence reflecting a significant higher HRQoL in the latter group. Participants educated up to secondary level reported a significant lower HRQoL on the emotions domain (*Mdn* = 3.5, IQR = 1.88) when compared with higher educated participants (*Mdn* = 4.31, IQR = 1.16, $p = .02$). The weight domain was not correlated with any of the baseline characteristics and additionally, none of the PCOSQ domains were significantly correlated with the BMI measured at the start of the LMP. The median VAS score for acne was 1.1 (6.4) reflecting a low level of perceived facial acne. However, there was a significant difference in median VAS score between participants with (*Mdn* = 6.65, IQR = 6.98) and without facial acne (*Mdn* = 0.8, IQR = 1.6, $p = .002$).

Effect of time on BMI, PCOSQ and VAS scores

During the LMP, participants lost on average one kilogram per month and the mean BMI decreased from 35.49±5.96 kg/m² to 33.78±4.84 kg/m² over a period of 24 weeks ($p = .27$). Furthermore, between

week 0 and 24, there was marginal evidence of a negative correlation between the decrease in BMI and the increase of the total PCOSQ scores (r = -.45, p = .06), the emotions domain (r = -.46, p = .05) and the body hair domain scores (r = -.41, p = .07).

Next, we report the results of the LMM analyses investigating the effect of time on the total PCOSQ score, the PCOSQ domain scores and the acne VAS score separately (Table 5). We observed a significant positive effect of time on the total PCOSQ score (F(2,37.5) = 23.7, p < .001), the emotions (F(2,37.9) = 4.2, p < .05), weight (F(2,42.1) = 24.8, p < .001), body hair (F(2,35.6) = 3.3, p < .05) and infertility problems domain scores (F(2,43.1) = 15.64, p < .001) over a time period of 24 weeks. This increase was each time significant between week 0 and week 12, but not between week 12 and week 24 (Table 6). With regard to the menstrual problems domain, only a marginal increase in this domain score was observed over the period of 24 weeks (F(2,38.8) = 3.08, p = .057).

The effect of time on the emotions domain scores interacted with the educational level of the participant. Over the period of 24 weeks the significant increase in emotions domain scores was less pronounced for higher educated participants (mean predicted difference = 1.11, p < .001) when compared with lower educated participants (mean predicted difference = 2.2, p < .001). The effect of time on the body hair domain scores interacted with the mFG score. The significant increase of the body hair domain scores during the first 12 weeks of the LMP, was only there for participants with an average or higher than average mFG score (mean predicted difference = 0.79, p < .001 and mean predicted difference = 1.32, p < .001, respectively). For participants showing lower than average mFG scores, no significant differences were observed between each of the time points. The infertility problem domain scores were influenced by the presence of a current unfulfilled wish to conceive and by the parity. The presence of a current unfulfilled wish to conceive had a negative effect (F(1, 23.1) = 21.94, p < .001) while the presence of a child had a positive effect on the PCOSQ scores (F(1, 24.4) = 4.32, p < .05).

With regard to the influence of facial acne on the HRQoL, a positive evolution was observed over the 24-week period which interacted with age (F(2, 29.3) = 4.2, p < .05). The pattern of overall decrease was different for younger participants when compared with older participants. For instance, predicting average acne VAS scores for young women (using the 25th percentile of age), showed a significant decrease from week 0 to week 24 and from week 12 to week 24 (week 0 vs. week 24: mean predicted difference = -1.31, p < .01; week 12 vs. week 24: mean predicted difference = -0.76, p < .05). For older women (75th percentile of age), the significant decrease from week 0 to week 24 was primarily situated between week 0 and week 12 (week 0 vs. week 24: mean predicted difference = -1.88, p < .001; week 0 vs. week 12: mean predicted difference = -1.51, p < .001).

Discussion

In the current study, we investigated changes in BMI and HRQoL in overweight adult women with PCOS during a 24-week LMP, consisting of a diet, exercise and psychological subprogram. Our findings point to the following conclusions: Firstly, we observed an overall increase in women's HRQoL after 12 and 24 weeks of the LMP. This supports the findings of Harris-Glocker et al. (2010) and Thomson et al. (2010) that the HRQoL is increased at the end of a lifestyle modification period. Our findings also point to a second conclusion that the positive evolution of the HRQoL was primarily situated during the first 12 weeks of the LMP. This is in line with the study of Thomson et al. (2010) where they observed an important increase in PCOSQ domain scores during the first 10 weeks of a 20-week LMP. Despite this important increase in HRQoL during a short period of 12 weeks, it doesn't seem justified to shorten a LMP to that time period since there is still an increase in HRQoL after 12 weeks which is possibly not at its highest level after 24 weeks of LMP. Further, a period of 24 weeks of LMP could still be too short to achieve a long-term weight reduction and maintenance according to the study of Lally, van Jaarsveld, Pott and Wardle (2010), reporting that it can take up to 254 days to form a new habit. Additional research on this issue is therefore needed.

Furthermore, our results confirm that body weight, irrespective of the BMI, is a high concern in women with PCOS (Coffey et al., 2006; Vrbikova & Hainer, 2009). In addition, over the period of 24 weeks, there was a decrease of 5% in BMI and a trend towards a correlation between the decrease in BMI and the increase in HRQoL. This confirms the findings of Harris-Glocker et al. (2010) who observed a trend towards a correlation between the decrease in BMI and the increase in PCOSQ weight domain scores over a period of 24 weeks in a group of obese adolescent women with PCOS (r = -.333, p = .06). A similar correlation was found by Thomson et al. (2010) for the emotions and weight domain scores (r = -.35 and r = -.43, $p \leq .01$, respectively) in overweight and obese adult women with PCOS. These results suggest that a modest weight loss is sufficient to elicit an increase in HRQoL, in addition to its positive effects observed with respect to the endocrine and metabolic features of PCOS (Hoeger et al., 2004; Thomson et al., 2008).

In our study, the presence of visible hair growth appeared to be the least concern when compared with the other PCOSQ domains at the start of the LMP. We also observed a significant negative correlation between the presence of hirsutism and HRQoL similar to earlier findings by Harris-Glocker et al. (2010) and Mc Cook et al. (2005). There is evidence that lifestyle treatment leads to an amelioration of hirsutism (Moran, Hutchinson, Norman, & Teede, 2011), however, as the life span of hair follicles is six months, the effect of LMP on the presence of hirsutism can be adequately assessed only after this time period (Castelo-Branco & Cancelo, 2010). Interestingly, we observed a positive

evolution of the body hair domain scores over the whole study period. This cannot be confirmed by the study of Thomson et al. (2010), where no significant evolution in body hair domain scores was observed over the 20-week study period. In our study, the increase in body hair domain scores was significant during the first 12 weeks of LMP, followed by a decrease during the second half of the program.

Since acne is also a clinical sign of hyperandrogenism, some studies have highlighted the necessity to include the presence of visible acne in the evaluation of the HRQoL of women with PCOS (Harris-Glocker et al., 2010; Jones et al., 2004). Consequently, we assessed the influence of visible facial acne on the HRQoL of the participants. Indeed, we observed a significant improvement of the influence of acne on the HRQoL during the total length of the LMP. Our findings thereby underscore the importance of including acne as an additional indicator of treatment efficacy for HRQoL outcomes. In the future, an acne domain should be included in the PCOSQ and this modified version of the PCOSQ should be validated in a group of adolescent and adult women with PCOS.

A study by Elsenbruch et al. (2006) described that the level of education, among other parameters, is an important determinant of emotional distress in women with PCOS. Hence, we took this into account while performing all our analyses. Indeed, we observed a lower PCOSQ emotions domain score in secondary educated study participants at the start of the LMP. Also, the level of education had a significant influence on the effect of time on the PCOSQ emotions domain score.

Fertility problems are an important consequence of PCOS, especially in overweight women (Vrbikova & Hainer, 2009). In our study, 71% of the participants had an unfulfilled wish to conceive and 77% had never given birth at the start of the LMP. Forty-two percent had a fertility treatment during the LMP. Since McCook et al. (2005) describes that the delivery of a viable child has a significant impact on the infertility problems domain score of the PCOSQ, we adjusted the analyses of that domain for the variable parity. Additionally, we took the objective evaluation of the presence of a current unfulfilled wish to conceive into account as the PCOSQ infertility problems domain looks into the participant's subjective perception of fertility problems (Cronin et al., 1998). Three participants became pregnant during the LMP but that didn't affect the outcome measures.

Strengths and limitations

We used a prospective longitudinal within-subject design creating the possibility to study the effect of time at different moments in time and having the advantage to minimize the recall error (Polit & Beck, 2004). On the contrary, this had the disadvantage of inducing the Hawthorne effect (Polit & Beck, 2004). The fact that women knew they were under study could possibly have influenced the way they

felt, as well as the way they answered the questionnaire. Psychological therapy (i.e., CBT) was described by Shaw et al. (2005) to be important in weight loss programs in order to obtain a maximum effect, and it was therefore included in our LMP. However, the design of the current study did not allow to test the additional value of this subprogram to the LMP. Neither it was possible to evaluate the benefit of the other two components of this LMP (i.e., the diet and exercise subprogram). Therefore future research using a randomized controlled study design is needed.

We also have to acknowledge the small sample size of 31 women with PCOS and a large number of missing data at different moments in time. This was due to women who failed to complete the questionnaire, and due to women who dropped out during the LMP. This missing information resulted in an unbalanced data set. This limitation was partly accounted for by using a LMM analysis (Verbeke & Molenberghs, 2000; West et al., 2006). The small sample size might also be a reason for low Cronbach's alpha scores of the PCOSQ (Rouquette & Falissard, 2011).

The drop-out rate in our study was 25.8% which is much lower than the drop-out rate during the 20-week LMP performed by Thomson et al. (2010) (i.e., 55.32%). It is described that the risk of attrition is especially large when the length of time between points of data collection is long (Polit & Beck, 2004). Interestingly, in our study most drop-outs occurred during the first part of LMP although the time between the consultations was longer when the program progressed. On the other hand, this is in line with the Iannaccone et al. (2013) study which reports that the risk of attrition is especially large during the beginning of longitudinal studies. A study by Galletly et al. (2007) mentions that a better compliance is possibly related to better feelings of psychological well-being. This might have been an influencing factor for drop-out but we have not registered the reason for drop-out due to lack of follow-up data.

Implications for Practice

Several health professionals play an important role in treating and counseling overweight women with PCOS (i.a., physicians, nurses and midwives, psychologists). Based on results of our study, it is clear that HRQoL in overweight women with PCOS evolves positively during a 24-week LMP. Additionally, earlier research described the positive effect of lifestyle modification on physical parameters in women with PCOS (Hoeger, 2006; Hoeger et al., 2004; Huber-Buchholz et al., 1999; Norman et al., 2002; Tang et al., 2006; Thessaloniki ESHRE/ASRM-Sponsored Consensus Workshop Group, 2008). Nurses and midwives who come into contact with those women should be aware of this existing evidence and, consequently, they should inform women about the benefits of lifestyle modification in terms of HRQoL. Nurses and midwives could contribute to the provision of adequate care to women with PCOS by referring them to the professionals whom are part of a multidisciplinary lifestyle modification team

(i.e., physician, physiotherapist, dietician, psychologist). Furthermore, nurses and midwives may also play an active role by coordinating a LMP, encouraging women to participate in a LMP, and by supporting them to maintain a modified lifestyle.

Recommendations for Future Research

To determine if a psychological subprogram has an additional benefit to a LMP, a randomized controlled trial should be performed. In addition, a long term cost-effectiveness analysis is needed to make a decision about the acceptable length of LMPs in terms of weight reduction, weight maintenance, and HRQoL in overweight women with PCOS.

Conclusion

In summary, our findings indicate that the HRQoL of overweight adult women with PCOS evolved positively, especially during the first 12 weeks of a 24-week LMP, consisting of a diet, exercise and psychological subprogram. Based on these results as well as on the results of the study of Thomson et al. (2010), overweight adult women with PCOS should be encouraged to follow a lifestyle modification program in order to increase their HRQoL.

Table 1.

Schedule of consultation with the appropriate professional per subprogram during the 24-week lifestyle modification program (LMP)

	Week of LMP												
Subprogram	0	2	4	6	8	10	12	14	16	18	20	22	24
Diet subprogram	*		*		*				*				*
Exercise subprogram	*		*		*				*				*
Psychological subprogram	*		(*)		(*)		*		(*)		(*)		*

Note. (*) = extra consultation on demand of the participant.

Table 2.

Key content components for the diet, exercise and psychological subprogram

Subprogram	Key content components
Diet subprogram	Mild energy restriction (i.e., -450 to -850 Kcal/day)
	General dietary principles
	Daily dietary pattern of three principal meals alternated with three snacks
	Healthy food
	Balanced meal composition
	≥ 1.5 L of calorie free drinks per day
Exercise subprogram	Raising daily physical activity level through increasing number of steps per day
	Practicing sports
Psychological subprogram	Cognitive behavioral therapy
	Additional techniques:
	Problem solving
	Goal setting
	Increasing social support

Table 3.

Psychometric properties of the PolyCystic Ovary Syndrome Questionnaire (PCOSQ) and the acne Visual Analogue Scale (VAS)

	week 0		week 12		week 24	
PCOSQ	Cronbach's alpha coefficient					
Five domains						
Emotions	.74		.86		.84	
Weight	.83		.84		.93	
Body hair	.94		.95		.94	
Infertility problems	.73		.81		.92	
Menstrual problems	.57		.74		.80	
Total PCOSQ	.40		.65		.81	
VAS	*Mdn*	IQR	*Mdn*	IQR	*Mdn*	IQR
Acne problems	1.1	6.4	0.9	2.38	0.2	1.5

Note. IQR = interquartile range; *Mdn* = Median

Table 4.

Demographic and clinical characteristics of the participants at the start of the lifestyle modification program

Characteristic	*n*	*Mdn*	IQR	Frequency	%
Demographic characteristic					
Age in years	31	29	5		
Highest level of education					
Secondary education	29			7	24
Higher education	29			22	76
Clinical characteristic					
Gravidity	31			9	29
Parity	31			7	23
Current unfulfilled wish to conceive	31			22	71
Duration of unfulfilled wish to conceive in days	31	731	944		
Body mass index in kg/m²	31	33.74	7.8		
Irregular menstrual cycle	31			29	94
Presence of hirsutism	30			13	43
Presence of facial acne	31			15	48
Free testosterone in ng/dL	31	0.82	0.95		

Note. Mdn = Median, IQR = interquartile range. Gravidity = number of women who had been pregnant at least once, Parity = number of women who had given birth at least once.
Continuous measurements are summarized as Median (IQR) since they are not symmetrically distributed.

Table 5.

Fixed effects and their interactions for all models from the linear mixed effects analysis using restricted maximum likelihood estimation

Dependent variable	Predictor	b	*SE*(b)	*t*
PCOSQ domain				
Emotions	Intercept	4.40	0.23	19.50
	Time *(week 12)*	0.82	0.23	3.55
	Time *(week 24)*	1.11	0.24	4.63
	Age in years	-0.01	0.03	-0.35
	Secondary education *(yes)*	-1.06	0.45	-2.34
	Time x Education			
	Time *(week 12)* x Secondary education *(yes)*	1.33	0.50	2.67
	Time *(week 24)* x Secondary education *(yes)*	1.08	0.50	2.15
$R^2_{glmm(m)}$ = 31.79%				
$R^2_{glmm(c)}$ = 71.25%				
Weight	Intercept	2.45	0.25	9.76
	Time *(week 12)*	1.51	0.27	5.61
	Time *(week 24)*	1.75	0.27	6.37
	Age in years	-0.02	0.03	-0.71
	Secondary education *(yes)*	0.51	0.45	1.13
	Body mass index in kg/m²	-0.07	0.04	-1.86
$R^2_{glmm(m)}$ = 35.32%				
$R^2_{glmm(c)}$ = 63.18%				
Body hair	Intercept	4.79	0.33	14.59
	Time *(week 12)*	0.79	0.20	3.93
	Time *(week 24)*	0.53	0.20	2.62
	Age in years	-0.02	0.05	-0.43
	Secondary education *(yes)*	-0.09	0.65	-0.13
	mFG score	-0.19	0.04	-4.42
	Free testosterone level in ng/dL	0.12	0.18	0.67
	Time x mFG score			
	Time *(week 12)* x mFG score	0.08	0.03	2.58
	Time *(week 24)* x mFG score	0.03	0.04	0.79
$R^2_{glmm(m)}$ = 36.03%				
$R^2_{glmm(c)}$ = 87.59%				
Infertility problems	Intercept	4.09	0.35	11.81
	Time *(week 12)*	1.29	0.30	4.28
	Time *(week 24)*	1.57	0.31	5.11
	Age in years	0.01	0.03	0.32
	Secondary education *(yes)*	0.32	0.37	0.86

	Current unfulfilled wish to conceive *(present)*	-1.56	0.33	-4.71
	Parity *(yes)*	0.97	0.46	2.10
$R^2_{glmm(m)}$ = 52.66%				
$R^2_{glmm(c)}$ = 59.82%				
Menstrual problems	Intercept	5.61	1.07	5.26
	Time *(week 12)*	0.55	0.29	1.88
	Time *(week 24)*	0.68	0.30	2.30
	Age in years	-0.01	0.05	-0.25
	Secondary education *(yes)*	-0.76	0.61	-1.24
	Menstrual cycle irregularity *(present)*	-1.77	1.04	-1.70
$R^2_{glmm(m)}$ = 14.19%				
$R^2_{glmm(c)}$ = 65.29%				
Total PCOSQ	Intercept	3.72	0.20	18.79
	Time *(week 12)*	1.00	0.18	5.42
	Time *(week 24)*	1.19	0.19	6.22
	Age in years	0.001	0.03	0.03
	Secondary education *(yes)*	0.05	0.37	0.14
$R^2_{glmm(m)}$ = 25.91%				
$R^2_{glmm(c)}$ = 69.65%				
Acne VAS				
Acne problems	Intercept	1.13	0.59	1.92
	Time *(week 12)*	-0.32	0.40	-0.80
	Time *(week 24)*	-0.73	0.55	-1.34
	Age in years	0.08	0.08	0.96
	Secondary education *(yes)*	-0.79	0.74	-1.07
	Acne *(present)*	4.27	0.91	4.69
	Time x Age			
	Time *(week 12)* x Age in years	-0.19	0.07	-2.96
	Time *(week 24)* x Age in years	-0.12	0.08	-1.52
	Time x Acne			
	Time *(week 12)* x Acne *(present)*	-1.51	0.64	-2.36
	Time *(week 24)* x Acne *(present)*	-1.77	0.84	-2.11
$R^2_{glmm(m)}$ = 27.65%				
$R^2_{glmm(c)}$ = 93.08%				

Note. Parity was observed as a nominal variable answering the question "Have you already been pregnant at least once?". PCOSQ = PolyCystic Ovary Syndrome Questionnaire; mFG = modified Ferriman-Gallwey; VAS = Visual Analogue Scale. $R^2_{glmm(m)}$ = marginal R^2 (i.e., variance explained by fixed factors); $R^2_{glmm(c)}$ = conditional R^2 (i.e., variance explained by the entire model) (Nakagawa & Schielzeth, 2013).

Table 6.

Mean predicted score per PCOSQ domain and mean predicted acne VAS score at the start, and mean differences at 12 and 24 weeks of the lifestyle modification program

	week 0	week 0 vs. week 12		week 12 vs. week 24		week 0 vs. week 24	
Dependent variable		Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
PCOSQ domain							
Emotions	4.13	1.48**	[0.99, 1.97]	0.17	[-0.37, 0.71]	1.66**	[1.16, 2.15]
Weight	2.61	1.51**	[0.98, 2.04]	0.24	[-0.33, 0.80]	1.75**	[1.21, 2.28]
Body hair	4.86	0.79**	[0.40, 1.18]	-0.25	[-0.67, 0.16]	0.53*	[0.14, 0.93]
Infertility problems	3.31	1.29**	[0.70, 1.88]	0.28	[-0.37, 0.92]	1.57**	[0.97, 2.17]
Menstrual problems	3.80	0.55	[-0.02, 1.12]	0.14	[-0.48, 0.75]	0.68	[0.09, 1.26]
Total PCOSQ	3.38	1.00**	[0.64, 1.36]	0.18	[-0.21, 0.58]	1.18**	[0.81, 1.56]
Acne VAS							
Acne problems	2.60	-1.08**	[-1.70, 0.45]	-0.55	[-1.20, 0.11]	-1.62**	[-2.45, -0.80]

Note. Mean predicted outcome scores are calculated with typical values of the explanatory variables in each model (Fox, 2003). PCOSQ = PolyCystic Ovary Syndrome Questionnaire; VAS = Visual Analogue Scale; CI = confidence interval.

** $p < .01$. * $p < .05$ (Bonferroni corrected for multiple testing per domain).

Veerle De Frène is holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). Petra De Sutter is holder of a fundamental clinical research mandate by the Flemish Foundation for Scientific Research (FWO-Vlaanderen). Financial support was provided by Merck Serono and Artevelde University College Ghent.

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Chapter 5 GONADOTROPIN THERAPY VERSUS LAPAROSCOPIC OVARIAN DRILLING IN CLOMIPHENE CITRATE RESISTANT POLYCYSTIC OVARY SYNDROME PATIENTS: A RETROSPECTIVE COST-EFFECTIVENESS ANALYSIS.

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Gynecol Obstet Invest 2015. Epub ahead of print 2015 Mar 11.

Abstract

Background: Gonadotropin therapy and laparoscopic ovarian drilling (LOD) are treatment options for ovulation induction (OI) in clomiphene citrate (CC) resistant polycystic ovary syndrome (PCOS) patients. The current evidence on the cost-effectiveness of both treatments is scarce, conflicting and performed from different health-economic perspectives.

Methods: A retrospective health-economic evaluation was performed from a societal perspective in which human Menopausal Gonadotropin (hMG) therapy (n=43) was compared with LOD (n=35), followed by OI with CC and/or hMG if spontaneous ovulation didn't occur within 2 months. Data were collected till patients were pregnant, with a time limit of 6 months after the onset of treatment. Outcomes were expressed in ongoing pregnancy rate and the number of live-born children.

Results: The ongoing pregnancy rate was 21/35 (60%) after LOD and 30/43 (69.8%) after hMG treatment (relative risk 0.85, 95% CI 0.61-1.19). The societal cost per patient, up to an ongoing pregnancy, was significantly higher after LOD versus hMG treatment (adjusted mean difference €1073, 95% CI €180-€1967).

Conclusion: This economic evaluation based on real life data shows that the societal cost up to an ongoing pregnancy is less after hMG treatment when compared with LOD surgery in CC resistant PCOS patients.

Introduction

Both gonadotropins and laparoscopic ovarian drilling (LOD) are treatment options currently used for ovulation induction (OI) in clomiphene citrate (CC) resistant polycystic ovary syndrome (PCOS) patients [1-3]. These treatments are proven to be effective but entail important costs and possibly bring along short and long-term complications [4-7]. In 2004 two health-economic evaluations from a societal perspective comparing both treatment strategies were published [8, 9]. Farquhar et al. [8] concluded that LOD was the most cost-effective option, whereas van Wely et al. [9] found a comparable cost-effectiveness of both treatments. A health economic evaluation, performed alongside a long term follow-up study, by Nahuis et al. [10] concluded that LOD was the most cost-effective option from a public payer perspective.

The current evidence on the cost-effectiveness from the societal perspective of gonadotropin treatment versus LOD in CC resistant PCOS patients is scarce and conflicting. Therefore we assessed the cost-effectiveness of these treatments applying a societal perspective, including direct medical costs covered by the public payer and the patient as well as productivity loss and transportation related costs, all based on retrospectively collected real life data.

Materials and Methods

The study was performed at the Department of Reproductive Medicine of Ghent University Hospital and was authorized by the Ethics Committee of that hospital. Informed consent was not obtained but patient information was anonymized and de-identified prior to analysis. Seventy-eight patients with PCOS, according to the Rotterdam consensus criteria [11], who were subfertile for >1 year and CC resistant (i.e. failure to ovulate with CC 150 mg/day for 5 days), were included. Forty-three patients were treated with hMG and 35 patients underwent LOD, based on patient's informed choice. All patients, except one, were treated between 2000 and 2009.

To administer hMG (Humegon, Organon, Oss, The Netherlands or Menopur, Ferring, Aalst, Belgium) a low-dose step-up protocol with a starting dose of 37.5 IU/day was used. When 1 or 2 follicles were >18 mm diameter, ovulation was triggered with hCG 5000 IU (Pregnyl, Organon, Oss, The Netherlands). Patients had intercourse or in case of mild male subfertility, underwent intrauterine insemination (IUI), 36 to 40 hours later. LOD was performed with a diathermy needle making 5 to 12 holes (3-4 mm in diameter) in each ovary, depending on its size. A standardised monopolar coagulation current set at 30 Watt was used. If no spontaneous ovulation occurred within 2 months after LOD, OI with CC and/or hMG was started (fig. 1).

Data were collected from patient's medical files and collection ended when patients became pregnant or after maximum 6 months of treatment. Effectiveness of treatment was expressed in ongoing

pregnancy rate and the number of live-born children. A miscarriage was defined as a loss of the foetus before 12 weeks of gestation. To calculate the direct medical costs, the medical resource items used per patient (e.g. injection of drugs, hospital visit, transvaginal ultrasound, laparoscopy) were identified and multiplied with their unit cost. The latter information was obtained via the patient invoices or from the Belgian public insurer (National Institute for Health and Disability Insurance). To calculate the costs related to productivity loss, the number of days of work leave was estimated per patient and multiplied with the societal cost for one day of work leave (€217.57), which was based on a report from Securex, a social and employment service organization [12]. The unemployment rate in 2007 was taken into account to calculate this amount [13]. An outpatient visit was counted as half a day of work leave. The duration of the hospital stay and the recovery phase at home were also registered. Travel distances were estimated per patient and multiplied with a standard price of €0.2940/km (www.bibf.be) to calculate the transportation cost. Costs were expressed in Euro and prices of the year 2007 were used. If prices of the year 2007 were not traceable, the cost was inflated to that year using the Belgian health index data.

Statistical analysis

Independent samples t-tests, Mann-Whitney U, Chi-square and Fisher Exact tests were used where appropriate and the statistical significance level was set at $p < 0.05$. The primary outcome was the cost until an ongoing pregnancy and sensitivity analyses were performed to evaluate the influence of several cost items on this analysis. Additionally a scenario analysis was done to study the cost until 3 months postpartum, including the cost for both singleton and twin pregnancies. For the latter purpose, the costs of the perinatal period (i.e. between 12 weeks of gestation until 3 months postpartum) were retrieved from Gerris et al. [14] for both singleton and twin pregnancies. All cost analyses were performed by using multiple linear regression to adjust for confounding factors [body mass index (BMI) and LH:FSH ratio] and residual analyses confirmed the adequacy of the models. Where appropriate, an incremental cost-effectiveness ratio (ICER) was calculated along with 95% nonparametric bootstrap percentile intervals based on 10000 bootstrap resamples. This is a popular nonparametric technique for calculating CI, based on repeating the data analysis for each of 10000 samples that are randomly drawn from the available data set (with replacement) and evaluating the variability in analysis results from sample to sample [15]. Statistical analyses were performed using SPSS version 19.0; bootstrap confidence intervals (CI) were obtained using the package boot in RStudio Version 0.97.168.

Results

Patient characteristics per treatment strategy are reported in table 1 [16]. The patient characteristics were not significantly different between the two groups, except for primary subfertility which was significantly more prevalent in the LOD group when compared with the hMG group.. The effectiveness of each treatment strategy after 6 months is reported in table 2.

The LOD surgery necessitated 1.46±0.74 days of hospital stay, followed by a recovery phase of 7.06±2.01 days at home. The median number of days of work leave per patient after LOD was 10 (IQR 4.4) versus 5.5 (IQR 6.5) after hMG treatment ($p < 0.001$). After LOD, a mean of 2.5±1.36 cycles of OI were performed. In that group, 11/21 (52.4%) ongoing pregnancies were achieved with additional drug therapy (i.e. 9.66±4.46 tablets of 50 mg CC/cycle and 1162.5±1170.34 IU of hMG/cycle) and the other 10/21 (47.6%) were spontaneous ongoing pregnancies (i.e. 5 after timed coitus and 5 without cycle monitoring). In the hMG group, the average number of hMG cycles was 2.7±1.5 with 1131.61±646.25 IU/cycle.

The societal cost per patient was significantly higher after LOD versus hMG treatment (table 3). Respectively 60.6% and 42.3% of this cost was due to productivity loss. In the LOD and hMG group, the drug cost accounted for 6.7% and 44.1% of the total direct medical cost, respectively.

Observing the substantial contribution of the cost of productivity loss to the societal cost after LOD, a sensitivity analysis was done by reducing the cost of productivity loss with 25% and 50%. A 50% reduction of that cost would make LOD the least expensive option (i.e. €2778±€1249 per patient) for the society , although not significant ($p = 0.6$). The adjusted incremental cost per ongoing pregnancy for a hMG treatment versus LOD would then be €3879 (bootstrap 95% CI -€52077 to €54181). We also studied the sensitivity of the societal cost after LOD to a change in the amount of drugs, since only 11 (52.4%) patients of this group needed additional drug therapy to achieve an ongoing pregnancy. The drug cost was varied between 0% and 200%, but the societal cost was not sensitive to that variation.

In the scenario analysis where we included the published cost until 3 months postpartum for singleton and twin pregnancies, we obtained a total societal cost of €8004±€7143 per patient after LOD and €11105±€12560 per patient after hMG treatment (adjusted mean difference €1597, 95% CI -€7706 to €4511). The adjusted incremental cost per live-born child for a treatment with hMG versus LOD was €15816 (bootstrap 95% CI -€83714 to €112657).

Discussion

This study compared the cost-effectiveness of LOD with hMG treatment for OI in CC resistant PCOS patients.

No significant difference was found in ongoing pregnancy rate and in the number of live-born children between both treatment groups, which is in line with Farquhar et al. [5] and Bayram et al. [6]. In our research, we had no data to confirm whether patients underwent a hysterosalpingography or diagnostic laparoscopy before treatment was started, although Tsuji et al. [17] advised to perform a diagnostic laparoscopy when timing therapy as well as when controlled ovarian hyperstimulation fails. It is possible that the patency of both tubes was evaluated during laparoscopic surgery for ovarian drilling but this could not be confirmed as well.

Despite the use of a low-dose step-up protocol for hMG administration the number of twin pregnancies was highest in the hMG group. This is similar to Bayram et al. [6] where the number of twin pregnancies after gonadotropin therapy was even significantly higher compared to the LOD strategy (RR 0.11, 95% CI 0.01-0.88).

We found that the societal cost per patient up to an ongoing pregnancy was significantly higher after LOD versus hMG treatment. In contrast, van Wely et al. [9] found a comparable societal cost up to an ongoing pregnancy between the two treatment strategies and Farquhar et al. [8] concluded that LOD was the least expensive option in CC resistant PCOS patients. Both studies used a societal approach as well. In our study the societal cost was mostly ascribed to productivity loss after LOD, which was in turn mainly caused by a long recovery phase at home. Only a 50% reduction of the cost of productivity loss made LOD less expensive for the society than hMG treatment. In our study, we have no information to justify the duration of the recovery phase. Interestingly, transvaginal hydrolaparoscopic ovarian drilling (THLOD) has been associated with a productivity loss of maximum 3 days [18]. And since there is evidence that THLOD results in a similar ovulation and pregnancy rate as LOD and is associated with a low risk of intra- and postoperative complications, this technique might be a valuable alternative to LOD in order to reduce the societal cost of an ovarian drilling [18-21].

When considering the societal cost per patient until 3 months postpartum, LOD was the least expensive option. This is an important finding since in this calculation the cost of a multiple pregnancy – which might be up to 5 times higher than the cost of a singleton pregnancy [14, 22] - was taken into account. Although in our study, the number of multiple pregnancies was not significantly higher after hMG treatment when compared with LOD, when the additional cost of these pregnancies was included, this had a substantial influence on the societal cost. Our finding concerning this cost is in line with the

conclusion of Farquhar et al. [8] even though there were no multiple pregnancies included in that study. Furthermore, one has to be aware that the higher risk of complications (e.g. preterm birth) associated with a multiple pregnancy results in an increased prevalence of disabled children [14]. This induces a lifelong additional societal cost. Aside from this medical-induced financial impact, raising twins in general has a larger societal impact as well since costs are double (in most cases) at the same moment in time.

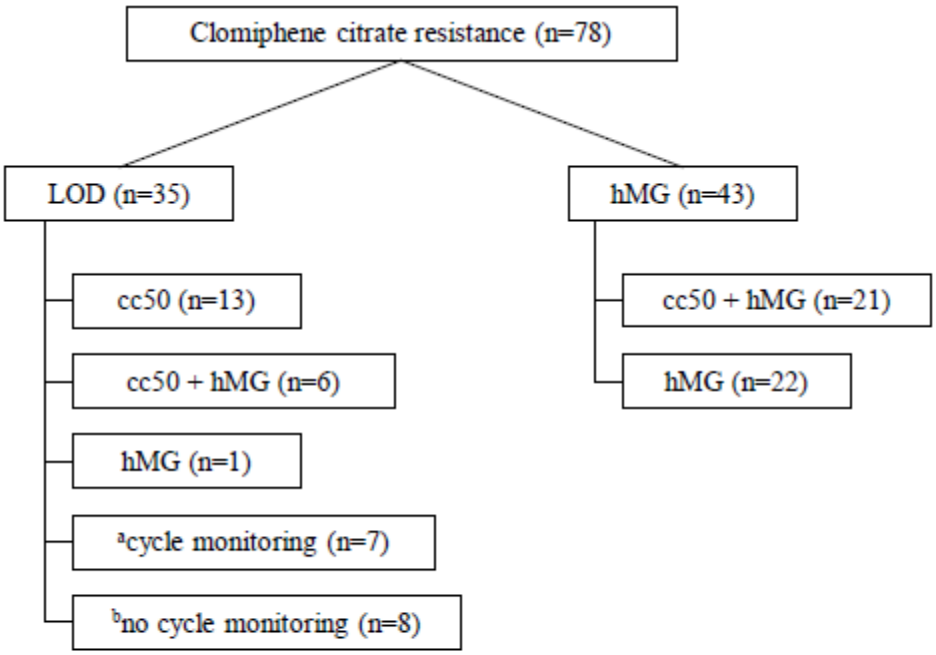
In the long term follow-up study by Nahuis et al. [23], performed over a period of 8 to 12 years, it was proven that laparoscopic electrocautery resulted in a higher prevalence of regular menstrual cycles and a higher spontaneous pregnancy rate when compared with gonadotropin therapy. The consequently lower need for OI or assisted reproductive technology (ART) lead to a lower mean cost per live birth after laparoscopic electrocautery when compared with gonadotropin therapy [10]. Although in this economic evaluation only a public payer perspective is considered, this is an important finding since the long term effectiveness and costs of both treatments were taken into account.

In our study, we have to acknowledge the small sample size of 78 patients, which is about half the sample size in the study of Bayram et al. [6], but is larger than in the study of Farquhar et al. [5]. We used a retrospective design having the advantage of avoiding the Hawthorne effect as well as protocol induced effects and costs [24]. Hence the real clinical practice (i.e. the real clinical and financial impact of a treatment) and not an idealized practice is reflected [25]. For clinicians as well as patients, it is important to base their clinical decisions also on such evidence in order to better manage uncertainty. Furthermore, there is also a growing interest in real life data on effectiveness and costs at the time when policy makers take reimbursement and pricing decisions [25]. On the other hand the non-randomized setting enhances the risk for confounding bias [24]. We attempted to reduce the influence of confounding factors on the calculated costs by regression adjustment for BMI and LH:FSH ratio, which were the sole two variables of clinical relevance having a significant influence on cost. Nevertheless we cannot exclude the possibility that the groups are not entirely comparable in terms of unmeasured factors. Even though the prevalence of primary subfertility was significantly higher after LOD, this variable did not have a significant influence on the cost analyses. We have to recognize that the mean BMI in our sample is < 30 kg/m². Moreover 76.7% and 66.6% of the LOD and hMG group, respectively, were not obese according to the WHO BMI classification (Table 1) [16]. This acknowledgement is important to make since in the general PCOS population up to 70% of the PCOS patients suffer from obesity [26]. A study by Amer et al. [27] proved that a BMI ≥ 35 kg/m² has an important negative influence on the efficacy of LOD. Therefore, one has to be careful when generalizing these results, also because the costs were calculated within the Belgian health care system. The mentioned incremental cost per ongoing pregnancy in the sensitivity analysis and per live-born

child in the scenario analysis should be interpreted with caution since the differences in both costs and effects are not significant [28].

We conclude that hMG treatment is the least expensive option for CC resistant PCOS patients from a societal perspective in terms of ongoing pregnancy. Only if the pre-, per- and postnatal period until 3 months postpartum is included, LOD is the least expensive option, although not significant. Considering the same time frame, further research is needed to make a statement about the cost-effectiveness of both treatments from a public payer and a patient perspective. Further research is also needed to assess the cost-effectiveness of both treatments from a societal perspective over a long term.

Figure 1: Flowchart of the treatments that participants received.



cc50 = clomiphene citrate 50 mg
[a]ovulation was monitored through transvaginal ultrasound and/or blood screening in view of timed coitus or non-stimulated IUI
[b]ovulation was not monitored.

Table 1. Patient characteristics of the study population per treatment strategy.

Characteristic	LOD (n=35)	hMG (n=43)	P-value
Age (years)	28.57±3.49	28.14±3.13	0.6
Body mass index (kg/m²)	24.4 (20.4-30)	23.4 (20.4-32.4)	0.9
BMI categories[a]			0.9
Underweight (< 18.5 kg/m²)	2/30 (6.7%)	3/42 (7.1%)	
Normal weight (18.5-24.9 kg/m²)	15/30 (50%)	20/42 (47.6%)	
Overweight (25-29.9 kg/m²)	6/30 (20%)	5/42 (11.9%)	
Obesity class I (30-34.9 kg/m²)	5/30 (16.7%)	9/42 (21.4%)	
Obesity class II (35-39.9 kg/m²)	2/30 (6.7%)	4/42 (9.5%)	
Obesity class III (≥ 40 kg/m²)	0	1/42 (2.4%)	
Hirsutism	11/18 (61.1%)	20/29 (69%)	0.6
LH:FSH ratio	2 (1.2-2.5)	1.5 (1-2.7)	0.7
Testosterone (ng/dL)	54.2 (36.5-85.2)	49.4 (38.5-64.8)	0.2
FAI	130.2 (75.5-266.4)	112.9 (48.2-214.6)	0.3
Insuline (µU/mL)	7.4 (4.2-16)	10.2 (6.2-26)	0.4
PCOM[b]	35/35 (100%)	38/43 (88.4%)	0.1
Irregular menstrual cycle	33/35 (94.3%)	39/43 (90.7%)	0.7
Primary subfertility	30/35 (85.7%)	28/43 (65.1%)	0.04
Smoking	5/29 (17.2%)	10/40 (25%)	0.4

[a]The international BMI classification of the World Health Organization is used [16].

[b]Polycystic ovarian morphology on transvaginal sonography.

Continuous measurements are summarized as mean±SD if symmetrically distributed, and as median (1st quartile - 3rd quartile) otherwise.

Nominal measurements are summarized as n(%).

Table 2. Effectiveness of each treatment strategy after a period of maximum 6 months.

Characteristic	LOD (n=35)	hMG (n=43)	RR	95% CI	P-value
Ongoing pregnancy rate	21/35 (60%)	30/43 (69.8%)	0.85	0.61-1.19	0.5
Twin pregnancy rate	1/21 (4.8%)	5/30 (16.7%)	0.29	0.03-1.96	0.4
Number of live-born children	22/35 (62.9%)	35/43 (81.4%)	0.77	0.57-1.03	0.3

Measurements are summarized as n (%).

RR = relative risk

Table 3. Mean (€) ± SD per patient up to an ongoing pregnancy of each cost type per treatment strategy.

Cost type	LOD	hMG	Adjusted mean difference	95% CI	Adjusted P-value
Societal cost[a]	3985±1677	3329±1864	1073	180 to 1967	0.02
(1) Direct medical cost covered by the public payer	1066±508	1139±765	13	-351 to 376	0.9
of which Drug cost	89±274	685±574	-555	-823 to -288	<0.001
(2) Total cost covered by the patient	504±413	784±491	-161	-401 to 78	0.2
(2a) Direct medical cost	358±287	508±286	-103	-245 to 40	0.2
of which Drug cost	6±17	41±34	-32	-48 to -17	<0.001
(2b) Transportation cost	146±172	276±246	-59	-176 to 58	0.3
(3) Cost related to productivity loss	2415±918	1407±735	1222	845 to 1599	<0.001
Total direct medical cost[b]	1424±746	1647±1006	-90	-563 to 383	0.7
Total drug cost	96±291	726±608	-587	-871 to -304	<0.001

[a] = (1) + (2) + (3)

[b] = (1) + (2a)

Veerle De Frène is holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO). Petra De Sutter is holder of a fundamental clinical research mandate by the Flemisch Foundation for Scientific Research (FWO). This research also received financial support by Merck Serono.

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Chapter 6 GENERAL DISCUSSION and PERSPECTIVES FOR FUTURE RESEARCH

The polycystic ovary syndrome is a chronic disease with a complex symptomatology wherewith the patient, as well as her family and the society have to deal. The general objective of this dissertation was to do research about psychological, perinatal, lifestyle and health-economic aspects of PCOS that really matter for the patient, her family and the society.

Firstly, our findings indicate that objective PCOS characteristics (i.e., parity, women's BMI, and current unfulfilled wish-to-conceive) as well as subjective PCOS characteristics (i.e., women's infertility-related and acne-related concerns) are associated with the sexual and/or relational satisfaction level of couples dealing with this chronic disease. Additionally, we found a differential association of these characteristics with the satisfaction level between women with PCOS and their partners.

Secondly, we observe an increased risk of preterm birth and an increased risk of giving birth to a baby with a higher birth weight in overweight versus normal weight women with PCOS having an ongoing singleton pregnancy.

Thirdly, our results show an improvement of HRQoL in overweight adult women with PCOS during a 24-week lifestyle modification program. This improvement is primarily situated during the first 12 weeks of LMP. Furthermore, despite the lack of significant changes in BMI, we found a trend towards a correlation between a decrease in BMI and an increase in HRQoL.

Finally, we found that, based on real life data, the societal cost up to an ongoing pregnancy was less after hMG therapy when compared with LOD surgery in CC resistant women with PCOS. However, when including the pre-, per- and postnatal period until 3 months postpartum, our results point into the direction of LOD being the least expensive option.

Further on in this chapter these results as well as methodological issues of this dissertation are discussed per research item.

6.1 Sexual and relational satisfaction in couples where the woman has polycystic ovary syndrome: a dyadic analysis.

6.1.1 Discussion

Relational functioning in intimate relationships is complex and is described in several theoretical frameworks. The vulnerability-stress-adaptation model of Karney & Bradbury (1995) is seen as the most complete and comprehensive model. According to that model, relational functioning is driven by adaptive processes (i.e., conflict and support) which directly influence the relationship quality and relationship stability. Also, these adaptive processes function as a mediator between stressful events and the level of relationship satisfaction. Stressful events might be related to the intimate relationship itself but may also be personal to one of both partners in an intimate relationship. The latter counts for couples in which one partner has (chronic) health problems (e.g., PCOS). The capacity of couples to cope with stressful events through the above mentioned adaptive processes depends on each couple member's strengths and vulnerabilities, as wel as on the kind and level of experienced stress (Karney & Bradbury, 1995; Bradbury & Karney, 2004).

Bradbury & Karney (2004) mention that marital quality is lower among couples experiencing higher levels of chronic stress. This is of interest in the context of PCOS being a chronic stressor in a couple's life. In contrast, our results report that the relational satisfaction levels of PCOS women and their partners were significantly higher when compared with a reference sample of heterosexual married women and men (Joseph et al., 2007). On the other hand, our results about the sexual satisfaction level were not unambiguous. More specifically, the sexual satisfaction levels of PCOS women and their partners were (not significantly) lower and higher, respectively, when compared with that reference sample (Joseph et al., 2007).

PCOS, as a chronic stressor, is characterized by important changes in a woman's physical appearance (i.e., hirsutism, acne, and overweight) which threaten her gender identity (Kitzinger and Willmott, 2002; Snyder, 2006). These changes in physical appearance are thought to have a negative impact on a couple's intimate relationship. Considering the objective measurement of hirsutism, acne, and overweight, we only found an association of overweight, as expressed by BMI, with the level of sexual and relational satisfaction. More specifically, our results are indicative for a negative association of PCOS women's BMI with their level of sexual and relational satisfaction. So far, in women with PCOS, the evidence about the association of overweight, as expressed by BMI, with sexual satisfaction and/or functioning is conflicting. Namely, a negative association, on the one hand, and the absence of an association, on the other hand, is described (Elsenbruch et al., 2003; Hahn et al., 2005; Månsson et al., 2011; Stovall et al., 2012). In the general female population, an increased BMI is not associated with a

decreased level of sexual satisfaction (Kadioglu et al., 2010; Yaylali et al., 2010). But, when using the parameters weight and waist circumference to define overweight, a significant negative correlation with the level of sexual satisfaction is detected (Yaylali et al., 2010; Brody and Weiss, 2013). To our knowledge, there is currently no evidence available about the association of a woman's BMI with her level of relational satisfaction in a sample of PCOS women as well as in the general female population wherewith our results could be compared. The same applies to the association of women's BMI with the level of sexual and relational *satisfaction* as experienced by their partners. However, the Boyes and Latner (2009) study concluded that male partners of heavier women judge their women to be less attractive. In contrast, our results suggest a higher level of sexual satisfaction in partners of PCOS women with a higher BMI when compared with partners of PCOS women with a lower BMI. This might probably be explained by the fact that one has a better self-image and self-esteem in the presence of a heavier sexual partner. Yet, the latter is only hypothetical and warrants further research. Our study is performed in a sample of overweight (BMI ≥ 25 kg/m²) women with PCOS. Although our study provides interesting new information about the association of women's BMI with the satisfaction level of both partners in a couple, our results can only be generalized to a population of couples dealing with PCOS where the woman is overweight.

Considering a woman's subjective perception of changes in physical appearance, we only found a significant negative association of the degree of acne-related concern with the level of sexual satisfaction in both women with PCOS and their partners. To date, there are no other studies in PCOS couples and in the general population reporting on the correlation of those concerns with sexual and/or relational satisfaction levels.

Besides the changes in physical appearance, subfertility is an important consequence of PCOS and is present in 55-90% of women with PCOS (Balen et al., 2005; Badawy et al., 2009). Our results suggest a positive association of subfertility (i.e., the presence of a current unfulfilled wish to conceive and the subjective infertility-related concern) with the level of relational satisfaction in both PCOS women and their partners. Although, the existing evidence about this association in a population of women without PCOS is inconsistent, it is described that knowing the cause of infertility has a significant positive impact on the relational satisfaction level in women (Bringhenti et al., 1997; Monga et al., 2004). Moreover, Månsson et al. (2011) mention that couples with fertility problems probably have a more stable relationship. This might interfere with the association of subfertility with the level of relational satisfaction. This indicates that one has to be careful when interpreting the results as reflecting the direct association of fertility problems with the level of relational satisfaction.

Weber (2011) describes that objective characteristics of a stressor (like PCOS) are conceptually and methodologically different from a person's perception of and reaction to a stressor. The fact that we found different associations of objective measurements of PCOS characteristics, on the one hand, and subjective measurements of PCOS characteristics, on the other hand, with the level of sexual and relational satisfaction, supports this statement. Weber (2011) and Trent et al. (2002) also describe that a person's subjective perception of a stressor is more directly related to one's individual and relational well-being than its objective characteristics. In our study, we found important associations of PCOS women's subjective experience of the syndrome with satisfaction levels which indicate that it is of interest to take into account the subjective perception of PCOS (as a chronic stressor). Unfortunately, in our study we were not able to attend the hypothesis that PCOS women's subjective perception of the disease-related characteristics was more strongly associated with the satisfaction level when compared with the objective measurement of the PCOS characteristics.

Our results show that the sexual and relational satisfaction level of women with PCOS was significantly lower when compared with their partners'. In contrast, the relational satisfaction level in patients with another chronic disease (i.e., kidney disease) was significantly higher than their partners' (Van Son-Schoones, 1994). A possible explanation therefor might be that PCOS has a worse impact on a patient's psychological well-being when compared with other (chronic) medical conditions (Coffey et al., 2006). On the other hand, the fact that PCOS might have a less negative impact on their partners' relational satisfaction level when compared with other chronic diseases can also not be excluded.

While studying the effect of a disease on the satisfaction level of both partners in a couple, one needs to take into account the interdependence of both couple members. This is important since two individuals involved in a committed intimate relationship are voluntary linked to each other and they socially interact with one another (Cook et al., 2006). This phenomenon makes them non-independent from each other (Cook et al., 2006). Consequently, a partner's experienced level of satisfaction does not simply reflect something about that single person but is driven in part by characteristics of the other one (e.g., a person's strengths and vulnerabilities, coping ability with a stressor) as well as by the established unique relationship between both partners in a couple (e.g., spousal support). Therefore, the measurement of a partner's level of satisfaction reflects the contribution of two individuals (Cook et al., 2006). This link between two partners in a couple is taken into account through performing dyadic statistical analyses (Cook et al., 2006). Using this analytic technique, our results show a significant differential association of PCOS characteristics with the satisfaction level between women with PCOS and their partners.

The effect of a stressor (e.g., PCOS) on a couple's relationship satisfaction might, besides the interdependence of both members in a couple, also be confounded or mediated by other external factors such as socio-cultural factors (e.g., culture and gender), experienced support by a professional and/or family, and other medical conditions whether or not related to the stressor (e.g., depression) (Elsenbruch et al., 2003; Berg and Upchurch, 2007; Kadioglu et al., 2010). It is important to adjust for such confounding factors in further research in order to clarify that the association found is reflecting a direct association.

6.1.2 Perspectives for future research

Although our results are promising, some limitations of this study must be addressed in order to clarify already existing as well as new research questions.

Firstly, a larger confirmatory study is needed to avoid that certain associations, representing statistically low to medium effects of PCOS on the satisfaction level, cannot be detected due to a too small sample size and the resulting lack of power. *Furthermore*, it is advised to include overweight as well as normal weight women with PCOS in future research. This would help to clarify the association of overweight with sexual and relational satisfaction, as well as to enhance the generalizability of the results to the general population of couples dealing with this chronic disease. *Also,* further research should take into account the influence of possible confounding and mediating factors.

Secondly, one should investigate if subjective rather than objective PCOS characteristics are more strongly associated with the satisfaction level in couples dealing with PCOS by using a multivariate statistical analytic model that includes objective predictors (i.e., objective PCOS characteristics) and subjective predictors (i.e., PCOS-related concerns) simultaneously. This might indicate whereupon to focus when treating and counseling those couples.

Finally, it might be of interest to do research about how unique the associations found are for couples dealing with PCOS.

In general, research about the sexual and non-sexual aspects of a long-term intimate relationship in couples dealing with PCOS is very rare. Given the importance of sexuality during reproduction, this topic warrants more scientific attention.

6.2 A retrospective study of the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with polycystic ovary syndrome.

6.2.1 Discussion

Overweight is an important symptom in women with PCOS threatening their own health. On the other hand, overweight during the preconceptional period also entails an important risk for complications during pregnancy, delivery and the neonatal period and hence threatens the health of both mother and child. As such, overweight is associated with an increased prevalence of macrosomia in singletons of women with PCOS, as well as in the general female population (Sarwer et al., 2006; Han et al., 2011; Wahabi et al., 2014). Our results do not confirm this but they do report that the mean birth weight is significantly higher in overweight (3386±663g) versus normal weight (i.e., BMI < 25 kg/m²) (3251±528g) women with PCOS. Although, these results are statistically different, this difference doesn't seem to be of clinical relevance. We also found a significant increased risk to deliver a singleton before 37 weeks of gestation in overweight women with PCOS. This finding is new in studies performed in a sample of women with PCOS (Mikola et al., 2001; Turhan et al., 2003; Han et al., 2011). In the general female population, the existing evidence is conflicting with studies indicating a positive or no association of BMI with the risk of preterm birth (LaCoursiere et al., 2005; Nohr et al., 2007; McDonald et al., 2010; Khatibi et al., 2012; Cnattingius et al., 2013). Interestingly, Nohr et al. (2007) report a significant increased risk of induced preterm birth in obese women (BMI ≥ 30 kg/m²) when compared with normal weight women (18.5 ≤ BMI < 25 kg/m²) but that effect disappeared when the analyses were adjusted for obesity-related diseases (such as PE, hypertension, diabetes mellitus). The fact that we didn't adjust for obesity-related diseases can be a possible explanation for the difference with our results.

Pre-pregnancy overweight is described to be a significant predictor of GDM in the general female population (Sarwer et al., 2006). In women with PCOS, the evidence is conflicting. Mikola et al. (2001) and Turhan et al. (2003) indicate that pre-pregnancy overweight (BMI > 25 kg/m²) is a significant predictor of GDM, while de Wilde et al. (2014) showed that BMI, waist circumference and waist/hip ratio are no significant predictors of GDM. Our results are in line with the latter. Nevertheless, we have to recognize that we were probably not able to elucidate a difference due to the rather small sample size of our study and the subsequent lack of power. Moreover, due to the limited number of available data in our retrospective study, we were not able to make the diagnosis of, specifically, GDM since we had no information about the diabetic status of each woman before pregnancy and as such we used the term 'diabetes during pregnancy'.

Some research groups suggest the adverse influence of an increased maternal age and an active pre-pregnancy smoking behavior on the prevalence of very preterm birth, preterm labour and low birth weight (Lowe et al., 1998; Delbaere et al., 2007). Given this clinical relevance, we adjusted all analyses for these variables. Nevertheless, our results only showed that an increased maternal age and an active pre-pregnancy smoking behavior were significant predictors for diabetes during pregnancy and a shorter gestational age, respectively. Interestingly, the difference in DDP (p = 0.02) in the univariate analysis might partially and very carefully being attributed to a higher maternal age in overweight women with PCOS, being aware of the fact that this difference in maternal age was not significant.

All women included in this study had fertility problems. Maman et al. (1998) and Dhont et al. (1999) described a increased risk of preterm birth, CS and perinatal mortality in singletons after a fertility treatment with IVF/ICSI. Moreover, Malchau et al. (2014) found a differential risk of adverse perinatal outcomes between singletons born after IUI and IVF. Based on our results, we cannot confirm this evidence since the treatment-to-pregnancy was no significant predictor of any of the studied outcome parameters.

PCOS in itself has been proven to be a risk factor for a delivery by Caesarean section (Altieri et al., 2010). Our results only showed marginal evidence for a higher prevalence of CS in overweight versus normal weight (i.e., BMI < 25 kg/m²) women with PCOS. This is in contrast to the results of studies in the general population which proved that obesity is a (significant) risk factor for a delivery by CS (Heslehurst et al., 2008; Wahabi et al., 2014). Since, in the general female population, obesity is related to macrosomia which is in turn an indication for a delivery by CS, macrosomia might a mediator in the association of obesity with CS. Further research about that is warranted.

In this study, the BMI was used to define pre-pregnancy overweight. However, the waist circumference is evaluated as the best indicator of central obesity, which is common in obese women with PCOS (Norman et al., 2002; Diamanti-Kandarakis, 2007). An increased waist circumference (i.e., > 88 cm) is indicative of an increased metabolic risk and the latter might in turn enhance the occurence of complications during pregnancy (e.g., GDM) (Després et al., 2001; International Diabetes Federation, 2012). As such, using the waist circumference to define pre-pregnancy overweight might be a valuable alternative to BMI in studies investigating the influence of overweight on the pregnancy, delivery and neonatal outcome in women with PCOS.

Our study focused on the pregnancy, delivery and neonatal outcome in overweight versus normal weight (i.e., BMI < 25 kg/m²) women with PCOS. Apart from these short-term complications in children born from mothers with PCOS, it is also important to be aware of more long-term consequences for those children. More specifically, children of mothers with hyperandrogenic PCOS have an increased

risk of Pervasive Developmental Disorders, the prevalence of hyperinsulinemia might be increased at the end of the pubertal period in girls whose mother has PCOS, and the pre-pubertal serum AMH concentrations might be increased in daughters of mothers with PCOS (Sir-Petermann et al., 2006; Kent et al., 2008; Palomba et al., 2012). However, the influence of overweight in mothers with PCOS on these long-term consequences is not clear and warrants further research.

6.2.2 Perspectives for future research

These results provide interesting new information but they also induce some ideas for future research.

Firstly, it is advised to perform a larger confirmatory study since in our study some associations were possibly not detected due to a lack of power.

Secondly, it might be worthwhile to focus on one outcome parameter in a time and to take into account the influence of all variables related to that specific parameter. That way, one can develop predictive models for each specific outcome parameter in women with PCOS.

Thirdly, given the existing evidence about an adverse impact of overweight and obesity on complications in multiple pregnancies in the general population (Salihu et al., 2010; Simões et al., 2011; Dickey et al., 2012; Dickey et al., 2013), the target group should be extended with PCOS women having a multiple pregnancy.

Fourthly, it might be interesting to study the association of the pre-pregnancy waist circumference with the pregnancy, delivery and neonatal outcome. *Moreover*, the differential association of pre-pregnancy BMI and pre-pregnancy waist circumference with the pregnancy, delivery and neonatal outcome in women with PCOS could be evaluated.

Fifthly, based on the existing evidence that excessive GWG is associated with an adverse pregnancy, delivery and neonatal outcome in the general female obese population (Cedergren, 2006; Nohr et al., 2008; Bogaerts et al., 2012; Gavard and Artal, 2014), the question arises about a possible differential and/or cumulative influence of pre-pregnancy BMI and GWG in predicting the pregnancy, delivery and neonatal outcome in women with PCOS.

Finally, in future research a prospective design might be considered in order to enable the inclusion of extra relevant outcome parameters (such as GDM) which were reported in studies in the general female population, but were unattended in our retrospective study due to lack of available data.

6.3 Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program.

6.3.1 Discussion

The PCOS symptomatology has an important impact on women's HRQoL (Ching et al., 2007; Jones et al., 2008). Based on studies which used the PCOSQ, weight is described to be the domain of highest concern in women with PCOS (Guyatt et al., 2004; Jones et al., 2004; McCook et al., 2005; Coffey et al., 2006; Ching et al., 2007). Though that all women in our study had a BMI ≥ 25 kg/m² at the start of the LMP, our results support this finding. But, the baseline objective measurement of overweight (i.e., BMI) was not significantly correlated with any of the PCOSQ domains. In our study, the domain of lowest concern was the body hair domain. To date, there is conflicting evidence about the domain of lowest concern in earlier performed studies. Some studies confirm our finding (Jones et al., 2004; McCook et al., 2005), while other studies mention the emotion, menstrual problems and infertility problems domain as the domain of lowest concern (Guyatt et al., 2004; Coffey et al., 2006; Ching et al., 2007). The difference in these findings might possibly and at least partially be attributable to differences in demographic and clinical characteristics of the included study participants. Our results also show that a high level of infertility-related concern is significantly related to a low parity and the presence of a current unfulfilled wish-to-conceive. This is in line with the finding by McCook et al. (2005) which mentions that the delivery of at least one viable child is predictive for a lower level of infertility-related concern.

In addition to the five PCOSQ domains, our results indicate that the presence of facial acne has an important negative influence on the HRQoL of adult women with PCOS as measured by a Visual Analogue Scale. This is an important finding, especially since facial acne was present in ~50% of our study sample. The rather high prevalence of acne in a sample of adult women with PCOS in combination with its significant negative influence on their HRQoL supports the added value of incorporating a full-fledged acne domain into the PCOSQ. Jones et al. (2004) made the same suggestion based on an evaluation of the face validity of the PCOSQ by semi-structured interviews in 12 adult women with PCOS. More specifically, this evaluation determined that the absence of an acne domain is a serious shortcoming of the PCOSQ so that the questionnaire addresses all relevant issues concerning the impact of this syndrome on a patient's quality of life. During the item selection phase of the development of the questionnaire by Cronin et al. (1998) acne was not selected as an essential item. A lack of data saturation during that phase might be a possible explanation therefor. Neither the Cronin et al. (1998) study nor the Jones et al. (2004) study described the exact symptom profile of the women with PCOS who were interviewed in the context of evaluating the face validity. Hence, this

creates the presumption that the symptom profile of these women has influenced the non-selection of acne as an essential item for the PCOSQ.

The measurement of the HRQoL provides extra information from a patient's own perspective about the impact of a disease but also about the effectiveness of a treatment which might be of importance in the clinical-decision making process of both patients and health professionals (Cronin et al., 1998; Jones et al., 2002). The significant improvement of HRQoL that we observed over the total length of our LMP is in line with earlier findings (Harris-Glocker et al., 2010; Thomson et al., 2010). We observed that this improvement was primarily situated during the first part of the LMP which also corresponds to the study by Thomson et al. (2010). To date, there is no existing evidence describing the ideal length of LMP, which might probably be very individual and depending on the desired HRQoL level one wants to reach. Nonetheless, it doesn't seem justified to shorten the duration of LMP to a time period of 10 to 12 weeks since in most treatment groups of the Thomson et al. (2010) study as well as in our study, there is still an increase of HRQoL after that time period, although not significant in our study. Moreover, the level of HRQoL is possibly even not at its highest level after 24 weeks of LMP. Also in terms of weight loss, which was moderate over the total length of our LMP, a period of 24 weeks could still be too short to achieve a long-term weight reduction and maintenance since a study by Lally et al. (2010) has proven that it can take up to 254 days to form a new habit.

The length of a lifestyle modification program also has an influence on the adherence to the program. In general, a high drop-out rate is common in long-term health promotion trials (Toft et al., 2007; Groeneveld et al., 2009). While this phenomenon is also described in lifestyle modification trials in women with PCOS, the total drop-out rate in our study (i.e., 25.8%) was less when compared with, for example, the study by Thomson et al. (2010) (i.e., 55.3%). Attrition studies found that the risk of attrition is especially large during the beginning of longitudinal studies (Iannaccone et al., 2013). This is in line with the results of our study, in which 75% of the participants dropped out during the first 12 weeks of LMP. Several factors are mentioned to be associated with drop-out: health problem-related items, dissatisfaction, depression, motivation towards lifestyle change, and length of time between points of data collection (Polit and Beck, 2004; Toft et al., 2007; Groeneveld et al., 2009; Iannaccone et al., 2013). Considering the latter, the risk of attrition is described to be higher as the length of time between points of data collection progresses (Polit and Beck, 2004). This is not the case in our study in which the frequency of the interventions (i.e., contact with the professionals) was highest during the first part of LMP, while that was the period counting most drop-outs. Unfortunately, we didn't investigate the reason of drop-out due to lack of follow-up. Anyhow, better knowledge about the mediating and confounding variables of participation and adherence to LMPs in overweight women

with PCOS, is essential to promote participation and to create a better basis for developing a tailored and effective lifestyle intervention approach (Toft et al., 2007).

Besides the ideal length of a lifestyle modification program, there is also no consensus about the ideal composition of such a program. The effectiveness of dietary interventions in terms of psychological well-being seems to depend on the dietary composition (Galletly et al., 2007). On the other hand, exercise is described to have a positive impact on one's psychological well-being irrespective of the type of exercise (Fontaine et al., 1999; Penedo and Dahn, 2005), and Liao et al. (2008) found that a self-directed walking program significantly reduced the level of body image distress in overweight and obese women with PCOS. In contrast, the Thomson et al. (2010) study found that exercise had no additional effect to diet only in terms of HRQoL in women with PCOS. In terms of short-term weight reduction, an intervention of diet only and of diet in combination with exercise seem to be equally effective. But, in terms of long-term weight reduction, the combination of diet and exercise is described to be the most effective option. An intervention focused on exercise only is less effective than a combination of diet and exercise in terms of short-term as well as long-term weight loss (Johns et al., 2014). Concerning a psychological intervention, Shaw et al. (2005) concluded that CBT should be part of a multi-component weight loss program in order to obtain a maximum effect. Therefore we added CBT to our LMP. However, since we used a prospective within-patient follow-up design, we were not able to draw a conclusion about the additional value of this psychological subprogram in terms of HRQoL.

Lifestyle modification is proven to result in a considerable weight reduction (Tang et al., 2006; Thomson et al., 2008) but, in our study, the decrease of the BMI was not significant after 24 weeks of LMP. Considering the negative effect of overweight and obesity on PCOS women's HRQoL (Jones et al., 2008), one should expect weight loss through lifestyle modification to be correlated with an increase in HRQoL. As such, the Thomson et al. (2010) study observed a significant correlation between a reduction in body weight and a HRQoL improvement in overweight and obese adult women with PCOS. Our results also showed a trend towards such a correlation. Taken together, these data suggest that a modest weight loss is sufficient to elicit a substantial increase in HRQoL. However, we must take into account that weight loss is possibly not the only factor that influences the change in HRQoL during LMP.

Changes in PCOS characteristics, whether or not as a consequence of weight loss, might have confounded or mediated the change in HRQoL. For example, a change in the degree of hirsutism could have mediated the correlation between women's change in body weight and their change in body hair related concern. But actually, this can only be assessed adequately after a time period of at least six

months since the life span of hair follicles takes that long (Castelo-Branco and Cancelo, 2010). Otherwise, one should also expect a confounding influence of pregnancy on a woman's HRQoL. In our study, three women became pregnant during the LMP, but the outcome measures (i.e., BMI and HRQoL) between pregnant and non-pregnant women were not significantly different. Also, undergoing a fertility treatment might have a negative influence on the change of HRQoL in women with PCOS during an LMP (Moll et al., 2012; Heredia et al., 2013). And finally, psychological problems (such as depression), which are described to be more prevalent in women with PCOS when compared with women without PCOS (Moll et al., 2012), may mediate the association between lifestyle modification and HRQoL. Moreover, it is described that a good emotional wellbeing is associated with better adherence to the program, which might probably lead to a more successful program in terms of weight loss (Galletly et al., 2007).

6.3.2 Perspectives for future research

Our study provides interesting information about the change in HRQoL and BMI during lifestyle modification, but our results also give rise to some suggestions as well as some new research questions.

Firstly, based on the results of this study as well as on the results of the study about the association of PCOS with couples' satisfaction level, we suggest to incorporate a full-fledged acne domain in the PCOSQ and subsequently evaluate the psychometric properties of the modified version of the PCOSQ.

Secondly, it might be of interest to investigate the added value of a psychological intervention (i.e., CBT) in LMP in terms of HRQoL.

Finally, a larger study over a longer period of time followed by an adequate follow-up can be performed in order to investigate the most ideal length of LMP in terms of weight loss and weight maintenance, on the one hand, and in terms of HRQoL improvement and HRQoL maintenance, on the other hand. *Additionally*, the influence of confounding and mediating factors (such as the evolution of objective PCOS characteristics, pregnancy, fertility treatment and psychological morbidities) should be taken into account.

6.4 Gonadotropin therapy versus laparoscopic ovarian drilling in clomiphene citrate resistant polycystic ovary syndrome patients: a retrospective cost-effectiveness analysis.

6.4.1 Discussion

Laparoscopic ovarian drilling and gonadotropin therapy are both effective treatments in case of CC resistance in women with PCOS (Farquhar et al., 2012). In general, gonadotropin therapy is associated with an increased risk of OHSS and multiple pregnancies (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). The multiple pregnancy rate is described to be significantly lower after LOD when compared with gonadotropin therapy (Farquhar et al., 2012). In line with this, our results report a lower twin pregnancy rate after LOD when compared with hMG treatment, although the difference was not significant. The effectiveness of both treatments also depends on the patency of both tubes. Therefore a diagnostic laparoscopy is advised when timing therapy and controlled ovarian hyperstimulation fails (Tsuji et al., 2009). In our study, we could not assure that a diagnostic laparoscopy and/or a hysterosalpingography was performed.

Our CEA, based on real life data, resulted in different conclusions about the cost-effectiveness of LOD versus gonadotropin therapy when, on the one hand, the cost until an ongoing pregnancy and, on the other hand, the cost until live birth was considered. The primary outcome parameter of our CEA was the cost until an ongoing pregnancy since we only had retrospectively collected real life data until 12 weeks of gestation. To calculate that cost we applied a societal perspective, including costs covered by the public payer, costs covered by the patient, as well as costs related to productivity loss. Because we had detailed information about the costs covered by the public payer and the patient, we were able to report additionally the cost-effectiveness from the public payer and the patient perspective and to draw the following conclusions about this outcome parameter.. Our data suggest that LOD is more cost-effective from the public payer and patient's perspective. On the other hand, our results show that gonadotropin therapy is significantly the most cost-effective option from the societal perspective. The latter finding is in contrast to the van Wely et al. (2004) study which used the same outcome parameter and found a comparable cost-effectiveness of both treatment strategies. Considering the cost until live birth, our results tended to confirm earlier evidence reporting LOD as the most cost-effective option (Farquhar et al., 2004). This is an important finding since the ultimate goal of a fertility treatment is to achieve a live birth and not only to achieve an ongoing pregnancy. Moreover, as the cost of a multiple pregnancy might be up to 5 times higher than the cost of a singleton pregnancy (Gerris et al., 2004; Lukassen et al., 2004), it is clinically more relevant to investigate the cost until live birth which comprises not only the treatment related costs but the costs related to the subsequent

pregnancy, labour and delivery as well. Furthermore, a multiple pregnancy is related to an increased risk of complications during pregnancy, labour and delivery (e.g., preterm birth) which possibly results in lifelong additional costs due to a higher prevalence of disabled children (Gerris et al., 2004). In general, raising twins also has a larger societal impact since costs are mostly double at the same moment in time. Apart from the impact of multiple pregnancies, the influence of complications due to treatment (e.g., postoperative infection after OD) should be considered. Since our results are based on real-life data, costs related to possible complications were taken into account. Nevertheless, we did not specifically identify what complications and how many complications occurred. As such, we cannot give a picture of the added cost due to treatment-related complications. In general, all consequences should be taken into account when the cost-effectiveness of LOD versus gonadotropin therapy is considered.

A study by Nahuis et al. (2011) describes that LOD is associated with a higher spontaneous pregnancy rate over a period of 8-12 years when compared with gonadotropin therapy. Consequently, this long term advantage of LOD resulted in a lower mean cost per live birth when compared with gonadotropin therapy (Nahuis et al., 2012). Although only the public payer's perspective was considered in that study this is an interesting finding.

In our study, loss of time at work was the main contributor of the increased societal cost of LOD surgery. A reduction of that absenteeism related cost by at least 50% had a substantial influence on that cost making LOD less expensive than gonadotropin therapy. So our results suggest that one must try to reduce this cost after LOD. Therefore, it might be of value to study the cost-effectiveness of THLOD, since this technique has been associated with a low productivity loss of maximum 3 days and its effectiveness is described to be similar to LOD (Fernandez et al., 2001; Shibahara et al., 2006; Badawy et al., 2009; Gordts et al., 2009; Catenacci and Goldberg, 2011). Additionally, although we have no information justifying the duration of the recovery phase, it seems an option to sensitize patients not to stay at home longer than necessary. Nevertheless, this might be difficult to achieve since LOD was already shown to be the most cost-effective option for the patient herself when the absenteeism related cost was not reduced with 50%. As such, the patients themselves will financially not feel a difference.

Our CEA is based on real-life data. This is especially interesting because that way the real clinical practice and not an idealized practice is reflected (Annemans et al., 2007). For health care providers as well as for patients, it is important to base their clinical decisions on evidence about the real clinical and financial impact of a treatment in order to better manage uncertainty (Annemans et al., 2007). In order to base our CEA on real-life data, we used a retrospective design having the advantage of

avoiding protocol-induced costs and effects, as well as avoiding the Hawthorne effect (Annemans, 2007). This is in contrast to the Farquhar et al. (2004) and van Wely et al. (2004) study, who performed prospective CEA's which were consequently protocol-directed and not a reflection of the daily clinical practice. In turn, these factors threaten the generalizability to women treated in a standard practice (Calvert et al., 2011). Nevertheless, a pitfall of the retrospective design we used, is selection bias through which we have to be aware of the possible influence of confounding factors. Hence, our analyses were corrected for clinically relevant variables that had a significant influence on the studied costs. In an attempt to bring together the positive aspects of a pro- and retrospective design to perform a CEA based on real life data, researchers are looking into the possibility to develop a new trial design, the so called "Real-World/EXPERIENCE trial" (Calvert et al., 2011).

There is evidence that obesity has a negative influence on the effectiveness of OI treatments and that class II obesity (BMI ≥ 35kg/m²) is an independent predictor of success of LOD surgery in terms of ovulation and pregnancy rate (Gambineri et al., 2002; Amer et al., 2004; Hirschberg, 2009). Our results confirmed that an increase of the BMI was significantly associated with an increase of all costs under study. Since an ovarian drilling through laparoscopic surgery might be a risky procedure in obese women when compared with normal weight women and because this procedure causes not seldom complications (e.g., bleeding) and/or failure to entrance in obese women (Gordts et al., 2009), it might be a more safe and successful option to perform an ovarian drilling through transvaginal access in those women.

Our CEA used clinical outcome parameters (i.e., ongoing pregnancy rate and number of live-born children) to assess the effectiveness of both treatments. Yet, it might be interesting to take into account the influence of both treatments on women's HRQoL. The study of van Wely et al. (2004) concluded that LOD as well as gonadotropin therapy don't really affect the HRQoL of the treated women. But, gonadotropin therapy was experienced to be a little more 'burdensome' when compared with the LOD strategy. In the study by Farquhar et al. (2002) the convenience and acceptability of both treatments was evaluated in women who underwent both treatment strategies. Their results show that 15/17 women (88.2%) preferred LOD for reasons such as 'easier and less traumatic' and 'easier in the sense that you go through one traumatic event only once' (Farquhar et al., 2002). Aside from these positive experiences in favor of LOD, the THLOD technique is 'scarless' which probably has a positive impact on a patient's long term quality of life (Gordts et al., 2009).

6.4.2 Perspectives for future research

Our study provides interesting new information about the cost-effectiveness of LOD versus gonadotropin therapy based on real-life data. However, there are still some items that have to be clarified and our findings also induce some new research questions.

Firstly, it is advised to perform a long term CEA based on real life data, taking into account long-term effects and subsequent costs of both treatment strategies. To create the most complete image, such a CEA should be performed from the societal perspective, making a clear distinction between the cost for the public payer, the patient and the absenteeism related cost.

Secondly, one should investigate the cost-effectiveness of a THLOD, especially as a way to reduce the absenteeism related cost and as a valuable and more safe alternative for obese women with PCOS.

Thirdly, given the high prevalence of central obesity and its impact on the reproductive function in women with PCOS as well as since the waist circumference is described to be the best indicator of central obesity, it seems relevant to study the influence of the waist circumference on the cost-effectiveness of LOD versus gonadotropin therapy in women with PCOS.

Finally, it might be of interest to perform a CEA using HRQoL as an alternative parameter for the effectiveness of both treatments and thereby considering THLOD as an alternative to LOD.

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Chapter 7 CONTRIBUTIONS OF THIS DISSERTATION and IMPLICATIONS FOR CLINICAL PRACTICE

The polycystic ovary syndrome is a complex and chronic disease that affects women at reproductive age, as well as their family and the society. This dissertation contributes to a better understanding of psychological, perinatal, lifestyle and health-economic aspects of PCOS that really matter for the patient, her family and the society. Health professionals (i.a., physicians, midwives and nurses, psychologists) should be acknowledgeable about this evidence and take this into account when treating and counseling women with PCOS. Furthermore, they have the task to inform women with PCOS adequately in order to help them with making joint clinical decisions.

More specifically, this dissertation suggests that PCOS, as being a stressor in a couple's life, is associated with their level of sexual and relational satisfaction. The satisfaction level of women with PCOS was found to be significantly lower than the satisfaction level of their partners. Interestingly, our results show an association of objective (i.e., parity, women's BMI and current unfulfilled wish-to-conceive) as well as subjective PCOS characteristics (i.e., women's infertility- and acne-related concerns) with the level of sexual and relational satisfaction in one or both partners. This stresses the importance to not only focus on the objective features of PCOS but also pay attention to women's subjective perception of the disease. As sexual and relational satisfaction are an integral part of a couple's life, health professionals should keep this evidence in mind when treating and counseling couples dealing with PCOS. This is especially important in couples with a wish-to-conceive since sexuality is an essential aspect of reproduction.

In addition to the negative impact of PCOS in itself on the perinatal outcome, this dissertation highlights the risk of preterm birth and giving birth to a baby with an increased birth weight in overweight women with PCOS having an ongoing singleton pregnancy. Although, we did not study the influence of overweight in multiple pregnancies, our results suggest the importance of pre-pregnancy weight loss in overweight women with PCOS in order to reduce the risk of adverse delivery and neonatal outcomes.

Furthermore, this dissertation confirms earlier evidence which describes that body weight has the worst impact on HRQoL in women with PCOS. Interestingly, the presence of acne was also found to have a significant negative impact on women's HRQoL. Our results showed that a moderate weight loss and a significant HRQoL improvement can be achieved through lifestyle modification in overweight adult women with PCOS. The latter was primarily situated during the first 12 weeks of a 24-week LMP. Although, we only observed a trend towards a correlation between weight loss and HRQoL improvement, these results support the encouragement of adult overweight women with PCOS to lose weight through lifestyle modification. Health professionals should refer those women to a multidisciplinary lifestyle modification team, and support them to maintain a healthy lifestyle.

Concerning the treatment of subfertile women with PCOS, this dissertation shows that both LOD and gonadotropin therapy are effective treatment strategies in CC resistant women with PCOS. Based on real-life data, our results indicate that LOD is the best option in terms of cost per ongoing pregnancy for the patient and the public payer. Moreover, our results tend to confirm that LOD is the most cost-effective option from the societal perspective if the cost per live-born child is considered. The latter is especially of interest since the additional cost for a multiple pregnancy is taken into account. Based on these results, women should be counseled towards LOD. Yet, given the high cost of absenteeism after LOD, one should consider other techniques (e.g., transvaginal hydrolaparoscopic ovarian drilling) to perform an ovarian drilling in order to shorten the duration of loss of time at work.

Chapter 8 **SUMMARY**

The polycystic ovary syndrome (PCOS) is a chronic disease which is present in up to 10% of women at reproductive age. The syndrome is characterized by an irregular menstrual cyle, polycystic aspect of one or both ovaries, clinical and/or biochemical signs of hyperandrogenism, overweight and subfertility. Through these characteristics, PCOS has an important negative impact on the physical and psychological well-being of these women. Also her family (partner, children) and the society are affected by this disease.

This dissertation has the aim to do research about psychological, perinatal, lifestyle and health-economic aspects of PCOS that really matter for the patient, her family and the society.

PCOS has a significant impact on women's health-related quality of life (HRQoL). Problems to maintain weight and problems to lose weight, in case of overweight, are the highest concern of those women. This is also confirmed by the results of our study. Additionally, the presence of acne in adult women with PCOS seems to have an important negative impact on their HRQoL. Since HRQoL is an important subjective marker of patient's well-being, it is important to be mindful of this evidence when treating and counseling women with PCOS.

Characteristics of PCOS also have a negative impact on several aspects of women's sexual life. As such, women with PCOS feel less attractive and have a lower level of sexual satisfaction when compared with women without PCOS. However, research about that topic is very limited and results are often conflicting. Our research focused on the association of PCOS characteristics with the level of sexual and relation satisfaction in couples dealing with this disease. The results show that the level of sexual and relational satisfaction is significantly lower in women with PCOS when compared with their partners'. Objective (i.e., parity, women's BMI and a current unfulfilled wish-to-conceive) as well as subjective characteristics (i.e., women's infertility- and acne-related concerns) are associated with the level of sexual and relational satisfaction in one or both partners. Although, partners live in continuous interaction with each other, the observed associations are clearly different between PCOS women themselves and their partners. Since sexual and relational satisfaction are an integral part of a couple's life and since sexuality is an essential aspect of reproduction in particular, these findings stress that health professionals should pay attention to this evidence when treating and counseling those couples.

About 30 to 70% of women with PCOS have to deal with overweight and obesity, which has a significant negative influence on the presence and severity of the PCOS symptomatology. The results of our study show that pre-pregnancy overweight in women with PCOS increases the risk of preterm birth and to give birth to a baby with a high birthweight. Although these findings are only applicable to singleton pregnancies, they suggest the importance of pre-pregnancy weight loss in overweight women with PCOS in order to reduce the risk of adverse delivery and neonatal outcomes.

Lifestyle modification is an effective strategy to lose weight. Moreover, weight loss through lifestyle modification has a positive effect on metabolic and hormonal parameters of women with PCOS. At present, there is an increased interest for the effectiveness of a treatment in terms of HRQoL. In our research, we observed a significant improvement of the HRQoL during an individualized 24-week lifestyle modification program (LMP), consisting of diet, exercise and cognitive behavioral therapy. Although, HRQoL improvement was significant over the total length of the LMP, this increase was primarily situated during the first part of the program. Based on these results, overweight women with PCOS should be encouraged to participate in a lifestyle modification program, and to maintain a healthy lifestyle.

Subfertility is a consequence of PCOS present in 55 to 90% of those women. The first line pharmacological therapy in women with PCOS is the administration of clomiphene citrate (CC), but 15 to 20% of those women are resistant for this drug. Then, a treatment with gonadotropins and a surgical ovarian drilling are effective alternatives, as confirmed by the results of our study. Based on real-life data, we showed that laparoscopic ovarian drilling (LOD) is the most cost-effective option for the patient and the health insurer in terms of cost per ongoing pregnancy. If the pre-, per- and postnatal period until 3 months postpartum are included, our results suggest that LOD is the most cost-effective options for the society. Since the latter includes the additional cost for a multiple pregnancy, women should be counseled towards LOD. However, since LOD is associated with a high absenteeism related cost, one shoul try to reduce this specific cost.

This dissertation confirms that PCOS has an important impact on the life of the patient and her family. Additionally, the syndrome has financial consequences for the whole society. Therefore, health professionals should take these results into account when treating and counseling women with PCOS. Further, women with PCOS should be informed adequately so they can pariticpate in making joint clinical decisions.

Chapter 9 **SAMENVATTING**

Het polycystisch ovarium syndroom, kortweg PCOS, is een chronische aandoening die tot 10% van de vrouwen van reproductieve leeftijd treft. Het syndroom wordt gekenmerkt door een onregelmatige menstruele cyclus, een polycystisch beeld van één of beide ovaria, klinische en/of biochemische tekenen van hyperandrogenisme, overgewicht en subfertiliteit. Via deze kenmerken heeft het syndroom een belangrijke negatieve impact of het fysieke en psychologische welzijn van deze vrouwen. Ook hun familie (partner, kinderen) en de maatschappij worden door deze aandoening getroffen.

Dit proefschrift heeft tot doel om onderzoek te doen naar psychologische, perinatale, lifestyle en gezondheids-economische aspecten van PCOS die belangrijk zijn voor de patiënt, haar familie en de maatschappij.

PCOS heeft een belangrijke impact op de gezondheidsgerelateerde kwaliteit van leven (in het Engels: health-related quality of life [HRQoL]) van de getroffen vrouwen. Problemen met behoud van gewicht en gewichtsverlies, in geval van overgewicht, blijken hun grootste bezorgdheid. Dit wordt ook bevestigd door de resultaten van ons onderzoek. Daarenboven blijkt de aanwezigheid van acne bij volwassen vrouwen met PCOS een belangrijke negatieve impact te hebben op hun HRQoL. Aangezien HRQoL een belangrijke subjectieve parameter is voor het welzijn van de patiënt is het belangrijk om deze resultaten indachtig te zijn bij de behandeling en begeleiding van vrouwen met PCOS.

Kenmerken van PCOS hebben ook een negatieve impact op verschillende aspecten van het seksuele leven van de vrouw. Zo voelen vrouwen met PCOS zich minder aantrekkelijk en ervaren zij een lagere seksuele tevredenheid in vergelijking met vrouwen zonder deze aandoening. Onderzoek hierover is echter nog zeer beperkt en resultaten zijn vaak ook tegenstrijdig. Ons onderzoek heeft zich toegespitst op het verband tussen enerzijds PCOS en anderzijds de graad van seksuele en relationele tevredenheid bij koppels die leven met deze aandoening. De resultaten tonen aan dat de graad van seksuele en relationele tevredenheid lager is bij vrouwen met PCOS in vergelijking met die van hun partners. Zowel de objectieve beoordeling van PCOS kenmerken (nl. pariteit, BMI van de vrouw en een actuele onvervulde kinderwens) als de subjectieve beoordeling van PCOS kenmerken (nl. de infertiliteit- en acne-gerelateerde bezorgdheid van de vrouw) wordt geassocieerd met de seksuele en relationele tevredenheid van één of beide partners. Hoewel geliefden in continue interactie leven met elkaar is de verscheidenheid van deze verbanden tussen de patiënten zelf en hun partners opvallend. Mede omdat de seksuele en relationele satisfactie integraal deel uitmaken van het leven van een koppel, benadrukken deze bevindingen dat hieraan voldoende aandacht moet worden besteed bij de begeleiding van deze koppels. En aangezien seksualiteit een essentieel aspect is van reproductie, blijkt dit vooral belangrijk in geval van een onvervulde kinderwens.

Ongeveer 30-70% van de vrouwen met PCOS heeft te kampen met overgewicht. Dit heeft een negatief effect op het voorkomen en de ernst van symptomen van deze aandoening. Uit de resultaten van ons onderzoek blijkt dat pre-conceptioneel overgewicht bij vrouwen met PCOS het risico op een preterme partus en de geboorte van een baby met een hoog geboortegewicht bevordert. Hoewel deze resultaten enkel van toepassing zijn op eenlingzwangerschappen, zijn dit belangrijke bevindingen op basis waarvan zwaarlijvige vrouwen met PCOS moeten worden geadviseerd om pre-conceptioneel gewicht te verliezen.

Het aanpassen van de levensstijl blijkt een effectieve manier om gewicht te verliezen. Daarenboven blijkt gewichtsverlies door middel van een 'lifestyle' modificatie programma een positief effect te hebben op metabole en hormonale parameters van vrouwen met PCOS. Meer en meer wordt echter ook belang gehecht aan de effectiviteit van een behandeling in termen van HRQoL. Zo wordt in ons onderzoek een significante stijging van de HRQoL waargenomen tijdens een 24 weken durend 'lifestyle' modificatie programma, bestaande uit dieetadvies, een oefenprogramma en cognitieve gedragstherapie. Hoewel de stijging van de HRQoL significant was over de volledige duurtijd van het programma, was deze stijging het sterkst tijdens het eerste deel. Op basis van deze resultaten zouden zwaarlijvige vrouwen met PCOS moeten worden aangemoedigd om deel te nemen aan een 'lifestyle' modificatie programma, alsook om een gezonde levensstijl aan te houden.

Subfertiliteit is een gevolg van PCOS dat voorkomt bij 55-90% van deze vrouwen. De medicamenteuze eerstelijns behandeling bij deze vrouwen is de toediening van clomifeen citraat (CC). Resistentie voor CC treedt echter op in 15-20% van de gevallen. Dan zijn twee andere behandelingen mogelijk: (a) een medicamenteuze behandeling met gonadotrofines, en (b) een chirurgische ovariële drilling. Beide behandelingen zijn effectieve alternatieven voor CC resistente patiënten, zo blijkt ook uit de resultaten van dit onderzoek. Op basis van 'real-life' data, hebben wij aangetoond dat een laparoscopische ovariële drilling (LOD) de meest kosteneffectieve optie is voor de patiënt en de zorgverzekeraar in termen van kost per doorgaande zwangerschap. Wanneer de kost van de zwangerschap, bevalling en postnatale periode mee in rekening wordt genomen, suggereren de resultaten van ons onderzoek dat LOD ook de meest kosteneffectieve optie is voor de maatschappij. Aangezien bij deze laatste berekening de extra kost voor een meerlingenzwangerschap in rekening wordt gebracht, zouden vrouwen moeten worden geadviseerd om te kiezen voor LOD. Anderzijds is deze chirurgische ingreep wel geassocieerd met een hoge kost voor ziekteverzuim dewelke men zou moeten proberen te drukken.

Dit proefschrift bevestigt dat PCOS een belangrijke impact heeft op het leven van de patiënt en haar familie. Daarenboven heeft dit syndroom ook financiële gevolgen voor de volledige maatschappij.

Daarom moeten gezondheidswerkers de resultaten van dit onderzoek indachtig zijn bij de behandeling en begeleiding van vrouwen met PCOS. Patiënten moeten daarenboven ook adequaat worden geïnformeerd zodat zij kunnen participeren bij het maken van klinische beslissingen.

Chapter 10 **LIST OF PUBLICATIONS**

A1 papers

De Frène V*, Verhofstadt L*, Loeys T, Stuyver I, Buysse A, De Sutter P. Sexual and relational satisfaction in couples where the woman has polycystic ovary syndrome: a dyadic analysis. *Hum Reprod* 2015;30:625-631. Epub 2014 Dec 22. Doi: 10.1093/humrep/deu342. [*Joint first authorship]

De Frène V, Vansteelandt S, T'Sjoen G, Gerris J, Somers S, Vercruysse L, De Sutter P. A retrospective study of the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with the polycystic ovary syndrome. *Hum Reprod* 2014;29:2333-2338. Epub 2014 Jun 24. Doi: 10.1093/humrep/deu154.

De Frène V, Verhofstadt L, Lammertyn L, Stuyver I, Buysse A, De Sutter P. Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program. *J Obstet Gynecol Neonatal Nurs* 2015. Epub ahead of print 2015 Aug 18. Doi: 10.1111/1552-6909.12739.

De Frène V, Gerris J, Weyers S, Dhont M, Vansteelandt S, Annemans L, De Sutter P. Gonadotropin therapy versus laparoscopic ovarian drilling in clomiphene citrate resistant polycystic ovary syndrome patients: a retrospective cost-effectiveness analysis. *Gynecol Obstet Invest* 2015. Epub ahead of print 2015 Mar 11.

A4 papers

De Frène V, De Sutter P. Het belang van gewichtsverlies in de behandeling van obese vrouwen met het polycystisch ovarium syndroom. *Tijdschrift voor vroedvrouwen* 2010;16:154-158. [Publication in Dutch]

Conference abstracts

De Frène V, Embo M, Gerris J, Weyers S, Dhont M, Annemans L, De Sutter P. Health-economic comparison of gonadotropin injections with electrocautery of the ovaries in clomiphene citrate resistant polycystic ovary syndrome patients. Oral presentation of abstract at 18th Scientific meeting of BSRM, Brussels, Belgium, October 26, 2007.

De Frène V, Embo M, Gerris J, Weyers S, Dhont M, Annemans L, De Sutter P. Health-economic comparison of gonadotropin injections with electrocautery of the ovaries in clomiphene citrate

resistant polycystic ovary syndrome patients. Poster presentation of abstract at 24th Annual meeting of ESHRE, Barcelona, Spain, July 6-9, 2008.

De Frène V. 'Life style modification' in de behandeling van obese vrouwen met het polycystisch ovarium syndroom. Oral presentation at 4th International Chair Francine Gooris, Ghent, Belgium, February 25-26, 2010. [Abstract in Dutch]

De Frène V, Verhofstadt L, Lammertyn J, Buysse A, De Sutter P. A study of the health-related quality of life in overweight and obese adult women with the polycystic ovary syndrome during a lifestyle modification program. Oral presentation of abstract at 29th Annual meeting of ESHRE, London, United Kingdom, July 8-10, 2013.

De Frène V, Vansteelandt S, T'Sjoen G, Gerris J, Somers S, Vercruysse L, De Sutter P. Pregnancy complications and perinatal outcome of obese versus non-obese PCOS women. Oral presentation of abstract at 30th Scientific meeting of BSRM, Genk, Belgium, November 15-16, 2013.

De Frène V, Verhofdstadt L, Loeys T, Stuyver I, Buysse A, De Sutter P. Couples dealing with the polycystic ovary syndrome: relational and sexual satisfaction. Oral presentation at "Stress" symposium, Ghent, Belgium, February 5, 2014.

De Frène V, Verhofdstadt L, Loeys T, Stuyver I, Buysse A, De Sutter P. The influence of the polycystic ovary syndrome on couples' relational and sexual satisfaction. Poster presentation of abstract at 30th Annual meeting of ESHRE, Munich, Germany, June 29-July 2, 2014.

Chapter 11 **DANKWOORD**

Aan het einde van deze langdurende, maar niettemin leerrijke en noeste arbeid ben ik opgelucht en blij dat de bevalling van deze prachtige baby voorspoedig is verlopen. De steun van velen was hierbij onmisbaar. Daarom graag een woord van dank.

Danken doet deugd ! Dankjewel …

Petra, ik wil jou bedanken voor de kans die ik van jou kreeg om met dit project te starten. Bedankt voor de aangename en energieke samenwerking tijdens de voorbije jaren, jouw deskundige begeleiding, luisterend oor en begrip op persoonlijk moeilijke momenten, jouw geruststellende woorden als ik me weer eens druk maakte over een futiliteit. Jouw enthousiasme en geloof in dit project zijn voor mij mede een stimulans geweest om dit tot een goed einde te brengen.

Lieven, ik wil jou bedanken voor jouw constructieve en deskundige begeleiding tijdens dit project. Bedankt om mij geduldig maar kritisch een stukje van de gezondheidseconomische wereld te laten ontdekken en mede de meerwaarde van een “retrospectieve” kosteneffectiviteitsanalyse te verdedigen. Het was voor mij een boeiende reis.

Ik wil de leden van mijn begeleidingscommissie bedanken voor hun oprechte interesse in mijn werk. Jullie hebben mij elk vanuit jullie expertise geholpen om de “heterogene” inhoud van mijn proefschrift vorm te geven en ten gronde uit te werken.

De leden van de examencommissie wil ik bedanken voor hun kritische vragen en constructieve feedback. Dit zette me nog eens extra aan tot nadenken over inhoudelijke en methodologische aspecten van mijn werk.

Lesley, aan jou een speciaal woordje van dank. Jouw kennis en kunde, jouw kritische ingesteldheid en punctualiteit hebben me geholpen om enkele psychologische aspecten van PCOS te doorgronden, alsook om vaardiger te worden in het schrijven van een manuscript. Je hielp me om PCOS als “stressor” in het leven van veel vrouwen te lijf te gaan. Het was een plezier om met jou te mogen samenwerken. Ik heb veel van jou geleerd.

Wat is een doctoraatsstudent zonder een portie statistische ondersteuning. Ellen, jij was in den beginne mijn statistische hulp en toeverlaat. Jouw bijkomende uitleg en jouw bevestigingen, gaven me het vertrouwen dat ik het toch allemaal wel wat snapte. Stijn, naast de pogingen die ik zelf ondernam om doorheen de meervoudige statistische analyses te worstelen, wil ik jou danken voor jouw deskundige uitleg en advies. Onze overlegmomenten waren voor mij steeds zeer waardevol. Jan en Tom, de statistici van de psychologie; dank voor het uitvoeren van de statistische analyses op een

beperkt aantal gegevens. Verwonderlijk welke mooie en (op heden) toch wel unieke resultaten hieruit zijn voortgekomen. Jullie hebben mij elk vanuit jullie expertise nieuwe statistische inzichten verschaft.

Het team van het lifestyle programma, Isabelle, Veerle, Isabelle en Patrick; bedankt voor jullie oprechte interesse in dit project, de aangename en vriendschappelijke samenwerking en bovenal de grote flexibiliteit die jullie aan de dag hebben gelegd tijdens de uitvoering van het lifestyle programma.

Collega's van de Arteveldehogeschool en het UZ Gent, dank voor de interesse in het verloop van mijn doctoraatsproject en het "succes" dat jullie me terloops toewensten. Dit gaf mij telkens een duwtje in de rug om de moed niet te laten zakken en verder te gaan.

Dankbaarheid is het geheugen van het hart! Dankjewel …

Graag ook een woord van dank en een grote ruiker bloemen voor mijn familie en vrienden:

Ik vermoed dat jullie de PCOS-taal nog steeds niet machtig zijn maar toch toonden jullie oprechte interesse in mijn werk. Lieve familie en schoonfamilie, dank voor de emotionele en praktische steun die jullie ons in grote getale hebben geboden. Voor opvang van de kindjes konden wij ook altijd op jullie rekenen als ik me weer eens achter mijn computer verschool en Kristof met huishoudelijke taken werd opgezadeld. Lieve vrienden, waarschijnlijk vaak onbewust, maar jullie zorgden op tijd en stond voor de nodige afleiding. Onze uitjes en ons af en toe eens goed laten "gletchen" deden mij mezelf weer herkennen en beseffen dat er veel meer is dan werken alleen.

Het sieraad van mijn leven zijn mijn familie en vrienden die er vertoeven!

En last but not least een bijzonder dikke merci en een megadikke knuffel voor diegenen die mij het meest dierbaar zijn. De diamanten die mijn sieraad volmaakt maken.

Maxime, lieve grote jongen; de vele knuffels, jouw guitige lach, maar ook jouw kritische ingesteldheid en gevatte uitspraken zoals "nu niet weer werken hé mama", deden me deugd maar vooral ook zorgzaam toezien op een goed evenwicht tussen mijn werk en de zorg voor ons gezin. Anderzijds gaf jouw uitspraak "Als je goed werkt mama, dan krijg je van mij een prinsessendiploma" mij extra moed om deze eindmeet te bereiken.

Jasmijn, lieve poppemie; al ben je nog zo klein, je brengt al ontzettend veel vreugde in mijn leven. Jouw schaterlachjes, jouw verwonderlijke blikken, jouw energieke en enthousiaste zelve doen me zoveel

deugd en komen mijn relativeringsvermogen alleen maar ten goede. Als ik zie hoeveel jij op één jaar tijd al hebt geleerd dan hink ik fel achterop. Enorm hoe snel en spontaan jij iets leert. Het zou fijn zijn om te weten hoe een kind als jij dit doet. We zouden er ongetwijfeld nog veel kunnen van leren.

Kristof, lieve schat; bedankt voor het geduld dat je gedurende de voorbije jaren aan de dag hebt gelegd, jouw onvoorwaardelijke steun, oppeppende zinnetjes, er immer in blijven geloven. Zonder jouw steun was ik er nooit in geslaagd om dit project tot een goed einde te brengen. De quote “We did it” is hier dan ook meer dan op zijn plaats. Ontzettend bedankt daarvoor. Mijn dankbaarheid voor dit alles valt moeilijk in woorden uit te drukken.

Dankuwel mijn lieve schatten! Ik hou van jullie!

Jullie zijn de reden waarom mijn hart zo gelukkig is!

Chapter 12 **CURRICULUM VITAE**

Veerle De Frène was born in Kortrijk on 30 August 1982. She studied Midwifery at the Artevelde University College Ghent and obtained her bachelor's degree in 2003. Subsequently, she worked at the Maternity Ward of Hôpital Victor Jousselin in Dreux (France) for one year. Once back in Belgium, she went to Leuven to obtain her master's degree in Nursing and Obstetrics – Major Subject Obstetrics at KU Leuven in 2006.

Veerle started working at the Artevelde University College Ghent in September 2006. In November of the same year she started with research about psychological, perinatal, lifestyle and health-economic aspects of the polycystic ovary syndrome. From the very beginning the complexity of that syndrome caught her attention. The first two years she combined her research work with a part time teaching job. From November 2008 till August 2013 she worked full-time at the Artevelde University College Ghent, during what period the content of her job evolved from teacher to internship coordinator. During that period she continued working on her PhD project. From September 2013 until August 2014 Veerle was holder of a Special PhD Fellowship by the Flemish Foundation for Scientific Research (FWO-Vlaanderen) by which she had the opportunity to finalize her PhD project. Currently, Veerle is working at the Artevelde University College Ghent as a teacher and is responsible for research in the Midwifery program.

Through performing her job and research project, she acquired organizational, coordination and presentation skills, and she gathered knowledge and experience about project management, project coordination, performing multiple statistical analytic techniques and cost-effectiveness analyses.

Veerle is married to Kristof Faes and they have two children, Maxime and Jasmijn.