Validity of the association between periodontitis and female infertility conditions: a concise review

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Abstract

Hormones and inflammatory mechanisms are implicated with female reproductive function, including follicle maturation, ovulation, embryo implantation, and pregnancy. Periodontitis is a chronic inflammatory disease due to a polymicrobial disruption of the homeostasis and may be considered as a potential risk factor that affect female fertility. The role of periodontitis is becoming meaningful, with significant associations with polycystic ovary syndrome, endometriosis and bacterial vaginosis. Further, periodontitis is linked with known risk factors towards female infertility, such as age, obesity, and chronic kidney disease. This review aims to summarize the available evidence on the association between periodontitis and female infertility-associated conditions, and to discuss warranting steps in future research.

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Introduction

According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), infertility is defined as a condition where the reproductive system is incapable to secure a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Adamson *et al.* 2018). Moreover, a healthy woman at the time of conception is more likely to have a successful pregnancy and to deliver a healthy child (Stephenson *et al.* 2018).

In 2010, 48.5 million couples worldwide were estimated to be infertile (Mascarenhas *et al.* 2012), yet nowadays, infertility is anticipated to be increasing, affecting more than 186 million people (8–12% of reproductive-aged couples), and fluctuates according to the level of development of the country. Furthermore, 14.3 and 25% of the couples are affected in the Western world and in developing countries, respectively (Vander Borgh & Wyns 2018).

The consequences of infertility may hamper population growth (Vander Borgh & Wyns 2018) and could negatively impact on the marital relationship (Onat & Beji 2012), sexual satisfaction (Ramezanzadeh *et al.* 2006) and psychosocial well-being (Cousineau & Domar 2007). Besides, couples can also experience anger, sadness, anxiety, depression, guilt, shame, a feeling of loss of control and incompleteness, dysfunction coping strategies, altered self-esteem, social

isolation and increased marital distress (Cousineau & Domar 2007, Schmidt 2009, Omu & Omu 2010, Pélouquin *et al.* 2013).

Infertility is a multi-factorial and multi-faceted clinical condition for both members of a couple and can be categorized as primary or secondary. In females, primary infertility represents a woman that has never been diagnosed with a clinical pregnancy and meets the infertility criteria. Secondary female infertility refers to the inability to become pregnant or to carry a baby to term after a previous successful pregnancy (Zegers-Hochschild *et al.* 2017). Aging is a key negative factor for women fertility (Hart 2016), though other risk factors comprising lifestyle and environmental factors have been gaining some relevance (Vander Borgh & Wyns 2018).

Among the relevant factors for female infertility, oral health is key for maintaining and allowing vital quotidian functions. A recent review highlighted the urgent need to address oral diseases as a global health priority (Peres *et al.* 2019). In particular, oral diseases share common risk factors with several conditions and have recognized impactfulness, such as pain, reduced quality of life, family interference, loss of work productivity and required high costs for treatment (Peres *et al.* 2019). One of the most important group of oral conditions is periodontal disease which affect the periodontium.

The periodontium encompasses mineralized (alveolar bone proper and root cementum) and soft connective

tissues (periodontal ligament and gingiva) (Mark Bartold & Van Dyke 2013). Periodontal health is defined as an absence or very significant reduction of clinical signs of periodontal inflammation (Lang & Bartold 2018). Periodontal disease initially presents as gingivitis, a reversible inflammation of the periodontium's soft tissues, with gingival bleeding and swelling. If progresses, gingivitis might evolve to periodontitis (PD), which is a progressive destruction of the periodontium.

The pathogenesis of PD relies on a complex interdependent relationship between a dysbiotic biofilm and host response, and if untreated results in the loss of periodontal attachment (Meyle & Chapple 2015, Roberts & Darveau 2015, Tonetti *et al.* 2018). The symptoms start with reversible gum inflammation (Bartold & Van Dyke 2017, Murakami *et al.* 2018, Trombelli *et al.* 2018) to an exacerbated and uncontrolled inflammatory response from the innate and adaptive immune systems (Ebersole *et al.* 2013, 2017). Ahead, periodontal tissues are progressively destroyed in an irreversible fashion, causing tooth mobility and its loss (Darveau 2010, Tonetti *et al.* 2015, 2018, Kinane *et al.* 2017) (Fig. 1).

The systemic repercussions caused by PD are now well established, and occur when bacteria and their products pass through the gingival epithelial barrier, and then spread into the bloodstream causing infectious and inflammatory responses (Chan *et al.* 2017, Albandar *et al.* 2018) (Fig. 1).

The main cause of PD, that is biofilm accumulation, results from negligent oral hygiene habits. Smoking habits are a key risk factor for periodontal disease (Jansson & Lavstedt 2002, Johannsen *et al.* 2014, Buduneli & Scott 2018), though due to the common inflammatory pathways, PD is strongly associated with other clinical conditions including diabetes mellitus (DM), metabolic syndrome, high blood pressure, rheumatoid arthritis, cardiovascular disease, stress, among others (Preshaw *et al.* 2012, D'Aiuto *et al.* 2013, Nibali *et al.* 2013, Tonetti & Van Dyke 2013, Jepsen *et al.* 2018, Polak & Shapira 2018, Botelho *et al.* 2020a, Hussain *et al.* 2020, Machado *et al.* 2020a,b). Also, PD has significant impact on the quality of life yet it can be recovered after periodontal treatment (Buset *et al.* 2016, Botelho *et al.* 2020b).

Very recently, two systematic reviews have comprehensively linked PD with male infertility and erectile dysfunction (Práger *et al.* 2017, Kellesarian *et al.* 2018a,b). PD was found highly prevalent among infertile men and severe PD was associated with higher deterioration of sperm quality (Zhu *et al.* 2010). Moreover, men with PD are at increased risk of developing erectile dysfunction, oligozoospermia and concomitant asthenozoospermia than periodontally healthy individuals (Kellesarian *et al.* 2017, 2018b, Práger *et al.* 2017). Drawing parallels with male infertility, the association between PD and female infertility-related

conditions is important to discuss, and a comprehensive revision would be of great interest.

Notwithstanding, an important question that still remains is whether female fertility may influence the onset and progression of PD and if periodontal infection and consequent inflammatory burden may influence female infertility (Kassebaum *et al.* 2014). Thus, this review aims to summarize the available lines of evidence on the relation between PD and female infertility-associated conditions, as well the possible pathophysiological pathways.

Female infertility-related conditions and Periodontitis

PD produces a local (saliva and gingival crevicular fluid (GCF)) and systemic inflammatory response (Kjeldsen *et al.* 1993, Cekici *et al.* 2014, Barros *et al.* 2016, Stadler *et al.* 2016, Cardoso *et al.* 2018, Polak & Shapira 2018). This response triggers the production of cytokines, resulting in tissue destruction, immunological reactions and indirectly influences other systems (Garlet 2010, Gonzales 2015). Comprehensively, the association between the periodontal status and the female reproductive system seems difficult to follow. Notwithstanding, the secondary role of PD in other diseases might contribute to explain how it can compromise female fertility. PD has been linked to polycystic ovary syndrome (PCOS), endometriosis (EM), obesity, bacterial vaginosis (BV), chronic kidney disease (CKD), and age, which in turn are risk factors affecting the spontaneous probability of conception.

Polycystic ovary syndrome

PCOS is a genetically complex endocrine, reproductive and metabolic disorder, affecting 5–15% of women in reproductive age worldwide (Azziz 2016). It is characterized by hyperandrogenism with distorted gonadotropin secretory activity, hyperinsulinemia, hypothalamic-pituitary-ovarian (HPO) axis dysfunction, ovulatory and menstrual dysfunction, and the presence of polycystic ovaries (Hull 1987, Norman *et al.* 2007, Dumesic *et al.* 2015, McCartney and Marshall 2016, Lambertini *et al.* 2017, Macut *et al.* 2017, Greenwood & Huddleston 2019). Moreover, PCOS appears to be associated with increased metabolic syndrome (MetS), including type 2 DM and insulin resistance (Dunaif 1997, Macut *et al.* 2017, Greenwood & Huddleston 2019), dyslipidemia (Caserta *et al.* 2014, Mirza *et al.* 2014), cardiovascular disease (Osibogun *et al.* 2019), and nonalcoholic fatty liver disease (Paschou *et al.* 2020). Despite many theories, the etiology of this syndrome remains poorly understood.

Figure 1 Periodontal health and immune response in periodontitis. Schematics of healthy gingiva (A) and periodontitis (B). The oral microbiome is a complex form ecosystems and contribute to maintain health when the the interaction between host and pathogen is in equilibrium in the gingival sulcus and periodontal pocket site. In this healthy environment, the host have a protective response by the immunity system and commensal bacteria. The first line of the defense is the sentinel cells involving macrophages, dendritic cells and mast cells, securing for evidence of pathogen invaders (A). However, when the biofilm-host balance is lost, causing a dysbiosis and immune overreaction of the host to microbial presences. This imbalance depends on the variance of patient's genetic, immune and biofilm profiles, and results in a heightened inflammatory state with increased levels of cytokines that leads to the local resorption of alveolar bone by osteoclast. These inflammatory cytokines activate macrophages, neutrophils, and fibroblasts to generate reactive oxygen species (ROS), which ultimately results in tissue damage.

Growing evidence supports a relationship between PCOS and chronic infections through the increase of oxidative stress (OS), inflammatory burden, adhesion molecules and leukocyte response (Pawelczak *et al.* 2014, Porwal *et al.* 2014, Dos Santos *et al.* 2015, Victor *et al.* 2016, Saglam *et al.* 2017a) (Fig. 2). Accordingly, the relationship between PCOS and PD was initially based on its common association with MetS (Dursun *et al.* 2011). In the latter, PCOS women had higher levels of periodontal inflammation and destruction than non-PCOS females, with marked hallmarks of OS and glycemic dysregulation on GCF (Dursun *et al.* 2011). Indeed, DM and OS are well-established risk factors towards PD (Preshaw *et al.* 2012, Chen *et al.* 2019) and might be significant mediating factors in the PCOS-PD way. Additionally, MetS may play a key role by inducing systemic inflammation and insulin resistance (Nibali *et al.* 2013).

Later, the cascade of proinflammatory events was proposed as a possible interplay between PD and PCOS (Özçaka *et al.* 2012, 2013, Akcall *et al.* 2015, Akcalı *et al.* 2017, Kellesarian *et al.* 2017, Tong *et al.* 2019). Both diseases appear to act in a synergistic manner to increase the expression of proinflammatory cytokines

(Knebel *et al.* 2008, Özçaka *et al.* 2013), and the severity of PD might also be associated with the aggravation of PCOS (Porwal *et al.* 2014).

Comprehensively, the possible mechanism linking PD and PCOS is rooted in the chronic subclinical inflammation of both diseases (Escobar-Morreale *et al.* 2011, Tong *et al.* 2019). In other words, a chronic subclinical inflammatory status elevates the concentrations of proinflammatory markers (such as C-Reactive Protein (CRP), tumor necrosis factor- α (TNF- α), interleukin (IL)-6, IL-17, and matrix metalloproteinase-9) (Özçaka *et al.* 2012, 2013, Akcalı *et al.* 2013, Cekici *et al.* 2014) and potentiates an oxidative stress environment (through local oxidant status-like myeloperoxidase and nitric oxide) (Dursun *et al.* 2011, Akcalı *et al.* 2017). Consequently, the subclinical inflammation due to PCOS may worsen periodontal destruction, and in the opposite way, subclinical inflammation due to PD through direct invasion of periodontal microbiota might underpin the pathogenesis of PCOS. Additionally, PD management has been implicated in insulin levels control as periodontal treatment alleviated high glycemic levels (D'Aiuto *et al.* 2018), and therefore, uncontrolled PD may indirectly impact on PCOS clinical status.

Figure 2 Polycystic ovary syndrome (PCOS) pathophysiology and the role of periodontitis. In PCOS, luteinizing hormone (LH) is key for hyperandrogenemia, and gonadotropin-releasing hormone (GnRH) pulse generator is resistant to the negative feedback effects of progesterone. Therefore, high GnRH pulse frequencies favor the production of LH and limit the production of FSH, which promotes androgen production and interfere with normal follicular development. Still, PCOS is associated with insulin resistance, abnormal ovarian function and adrenal steroidogenesis, which contributes to hyperandrogenemia and female infertility. Further, PCOS women have higher serum levels of IL-6, TNF- α , C-reactive protein (CRP), and white blood cell count. The PCOS-PD association is proposed to be grounded with common systemic inflammation, oxidative stress (OS) and insulin resistance. Further, higher levels of sex steroid hormones in PCOS patients negatively impact periodontal health.

Still, PCOS is characterized by excessive levels of sex steroid hormones that have a negative impact on PD (Dursun *et al.* 2011, Porwal *et al.* 2014, Rahiminejad *et al.* 2015, Hameed & Ahmend 2017, Najah *et al.* 2017, Saglam *et al.* 2017, Işık *et al.* 2020) due to the presence of androgens, estrogen and progesterone receptors in the gingival tissues (Parkar *et al.* 1996, Gornstein *et al.* 1999, Kawahara & Shimazu 2003). It seems that estrogen and progesterone changes modify the gingival tissues, leading to a higher vascular permeability and decreased keratinization of the gingival epithelium (Parkar *et al.* 1996, Gornstein *et al.* 1999, Kawahara & Shimazu 2003).

Although several studies had shed light on the association between PCOS and PD, the relationship between PD and infertility in women with PCOS still remains to be fully elucidated (Kellesarian *et al.* 2017, Tong *et al.* 2019). Despite the lack of longer prospective studies, a recent investigation on women with both PCOS and PD has assessed the impact of PD treatment with standard Myo-inositol (MI) on systemic conditions (Deepti *et al.* 2017). The results of this randomised clinical trial showed that treating PD with MI reduced systemic inflammation and improved metabolic

parameters in comparison to a therapy only with MI (Deepti *et al.* 2017). However, this study did not consider how much PCOS women were infertile at the baseline and, therefore, was not able to retrieve if resolving PD could have influenced the fertility rate.

Nevertheless, the influence of PCOS-PD link on female infertility is reasonable and might be grounded in (1) PCOS is associated with hyperandrogenism, hyperinsulinemia, and increased OS levels and which in turn have a negative impact on periodontal inflammation and destruction; (2) PD triggers proinflammatory and OS levels that dysregulate insulin resistance and negatively impact ovarian function.

Obesity

The adipose tissue is no longer seen as a simple stock of energy but a complex endocrine organ that produces many pro-inflammatory adipokines including hormones (such as adiponectin, leptin, and resistin) and pro-inflammatory cytokines (such as TNF- α , IL-6) (Kern *et al.* 2003). CRP serum levels are positively correlated with BMI and obesity (Maiorino *et al.* 2018, Pavela *et al.* 2018). Therefore, obesity is considered to be a chronic

low-grade inflammatory state (Broughton & Moley 2017, Pavela *et al.* 2018, Sudhakar *et al.* 2018).

Obesity contributes to higher levels of insulin and consequently insulin resistance and appears to exacerbate the symptoms of PCOS (McCartney & Marshall 2016). Furthermore, obesity has a negative effect on female infertility by HPO axis (Broughton & Moley 2017, Slopian *et al.* 2019) and overproducing androgens (Rachoń & Teede 2010). These increased androgens are highly transformed in estrogen at the periphery due to excessive adipose tissue (Jungheim & Moley 2010). As a consequence, HPO axis is negatively feedbacked and affects gonadotropin secretion, resulting in menstrual irregularities, ovarian malfunction, and therefore, infertility states (Jungheim & Moley 2010, Rachoń & Teede 2010).

Similar to PCOS, obesity is also a risk factor for the onset and worsening of PD due to an excessive levels of sex steroid hormones and higher levels of systemic inflammation (Chaffee & Weston 2010, Keller *et al.* 2015, Broughton & Moley 2017, Martinez-Herrera *et al.* 2017, Khan *et al.* 2018). Obesity increases the risk for the colonization of red complex periodontal microorganisms, which in turn may further lead to the onset of periodontal inflammation (Suresh *et al.* 2017). A recent evidence-based study concluded that obese patients have 30% higher risk of having PD and patients with PD have an average difference of 2.74 kg/m² on BMI mean than non-PD patients

(Moura-Grec *et al.* 2014). Additionally, obese patients with PD have elevated TNF- α and IL-1B GCF levels compared to non-obese PD individuals and, therefore, a higher localized proinflammatory state (Akram *et al.* 2016) (Fig. 3).

An underlying common characteristic is the subclinical inflammation caused by obese states. As previously discussed in this review, a subclinical inflamed organism will contribute to worsen PD status (Suvan *et al.* 2011), and this might explain a possible mediation effect of PD on infertile conditions. Also, increased concentration of adipocytes may dysregulate immune responses (Falagas & Kompoti 2006) resulting in increased PD susceptibility and exaggerated host immune responses (Suvan *et al.* 2011).

However, the effect of obesity and PD simultaneously on female infertility is still yet to be fully clarified, and future studies should be performed to assess this possible association using multivariate logistic regression or even mediation analysis. Further, such association might be due to the increase of inflammatory cytokines and the inflammatory burden at the systemic level, which may hamper time to conception.

Endometriosis

EM is one of the most intriguing gynaecological diseases and remains a challenging condition to treat

Figure 3 Suggested hypothesis of periodontitis in obese patients may lead to ovarian dysfunction. Obesity and increased body mass index (BMI) in women stimulate multiple aspects of lipotoxicity, such as intracellular lipid accumulation, inflammatory responses, and oxidative stress (OS). Alter levels of adipokines, such as leptin, in the obese state can affect steroidogenesis and directly affect the developing embryo, and can alter the function of hypothalamic-pituitary-ovarian (HPO) axis. Further, obesity is related to higher circulating levels of insulin, which stimulus the ovarian production of androgen. These androgens are aromatized to estrogen at high rates in the periphery due to excess adipose tissue, leading to negative feedback on the HPO axis and affecting gonadotropin production. Furthermore, the excessive levels of sex steroid hormones are linked to PD, that in turn increases the periodontal inflammation and increases the OS. The sum of systemic inflammation induces inflammatory responses in other tissues including the ovary.

(Bullon & Navarro 2017). It is a chronic inflammatory and an oestrogen-dependent disorder (Giudice & Kao 2004, Burney & Giudice 2012, Hickey *et al.* 2014, Vercellini *et al.* 2014, Vallvé-Juanico *et al.* 2019), characterized by the presence of endometrial tissue outside the uterine cavity and mainly found attached to sites within the pelvic peritoneum (Giudice & Kao 2004, Greene *et al.* 2016). EM is estimated to affect 3–10% of women in the reproductive age group (Burney & Giudice 2012, Jiang *et al.* 2016) and also in 50–57% of infertile women (Kavoussi *et al.* 2009, Meuleman *et al.* 2009).

Infertility due to EM has been widely investigated and multiple pathways are on its cause, such as inflammatory processes, anatomical distortions, local endocrine alterations and OS (Van Langendonck *et al.* 2002, Agarwal *et al.* 2005, 2012, Gupta *et al.* 2006, De Ziegler *et al.* 2010, Visioli & Hagen 2011, Scutiero *et al.* 2017, Li *et al.* 2019).

An association between EM and PD has been proposed via inflammatory and OS mechanisms, though only two cross-sectional studies could provide such information (Kavoussi *et al.* 2009, Thomas *et al.* 2018). In particular, women suffering from EM had a 57% higher risk of having diagnosed PD (Kavoussi *et al.* 2009). Also, moderate-to-severe PD was found to be higher among women with EM (Thomas *et al.* 2018).

Similarly to the PD-PCOS association, EM also promotes a subclinical inflammatory status, with the increase of cytokines and pro-inflammatory markers such as IL-1 beta, IL6, IL-8, TNF- α , that might complicate PD condition with higher periodontal tissue destruction (Kavoussi *et al.* 2009, Cekici *et al.* 2014). On the other hand, no studies have investigated whether PD might contribute towards the onset or progression of EM. Nevertheless, the rationale that PD might be a direct cause of intrauterine and chorionic tissues infection through bacterial spreading has been demonstrated (Gonçalves *et al.* 2002, Barak *et al.* 2007, Katz *et al.* 2009, Fardini *et al.* 2010, Hasegawa-Nakamura *et al.* 2011). Therefore, the hypothesis that PD might trigger a local immune reaction aside with the installed subclinical inflammatory state in EM is conceivable though it shall be investigated indeed.

Bacterial vaginosis

Vaginal microbiota usually changes throughout the menstrual cycle and it depends on vaginal hygiene, sexual activity, use of intimate products, hormonal contraception, and lubricant use (Gajer *et al.* 2012). Nevertheless, greater microbiota stability is associated with the estradiol peak at ovulation and progesterone rise in the midluteal phase (Gajer *et al.* 2012).

The dysbiosis of vaginal microbiota can result in BV. This condition is highly prevalent, affecting nearly 30% of women during the reproductive years (Allsworth & Peipert 2007) and it is described by a decrease in the

commonly predominant *Lactobacillus* bacterial species, and an increase in anaerobic microbiome (Fredricks *et al.* 2005). Typically asymptomatic, the most common symptoms are discharge and odor (Klebanoff *et al.* 2006). Although not fully understood (Koumans *et al.* 2007), BV etiology is currently attributed to hormonal disturbances (Schwebke *et al.* 1996, Keane *et al.* 1997, Wilson *et al.* 2002). From the obstetric view, BV was associated with abortion (Ralph *et al.* 1999, van Oostrum *et al.* 2013, Isik *et al.* 2016, Carlsson *et al.* 2018, Haahr *et al.* 2019), implantation failure (Moreno *et al.* 2016), premature rupture of membranes and preterm birth (Yudin 2005). However, the link between BV and woman infertility is still not firmly established (van Oostrum *et al.* 2013, Haahr *et al.* 2019).

The female reproductive tract microbiota is not confined to the vaginal compartment but also in the uterus and endometrium (Swidsinski *et al.* 2013, Mitchell *et al.* 2015). Although endometrial microbiota has particular species and the bacterial load is significantly lower compared to vaginal area (Moreno *et al.* 2016, Bedaiwy 2019), vaginal microbiota appears to be an important source of ascending bacterial colonization (Swidsinski *et al.* 2013, Mitchell *et al.* 2015). BV was significantly related to tubal factor infertility among *in vitro* fertilization (IVF) patients (van Oostrum *et al.* 2013, Haahr *et al.* 2019). Despite these results highlighting the biological plausibility of bacterial ascending to the upper genital tract and cause subclinical infection and inflammation (Haahr *et al.* 2019), it is imperative to conduct more research before inferring a definitive causal relationship.

Some studies propose that the vaginal *Lactobacillus* genus produces lactic acid and short-chain fatty acids, and this homeostasis environment at pH ≤ 4.5 prevents the dysbiosis in healthy women (Skarin & Sylwan 1986, Yamamoto *et al.* 2009). The mechanism that occurs in the endometrium apparently does not have the same function because no correlation was found in the pH levels of endometrial fluid samples and endometrial microbiota (Moreno *et al.* 2016). Thus, it is important to assess how bacterial endometrial dysbiosis can trigger an inflammatory response, direct production of microbial metabolites and/or enzymes capable of inducing major cell pathways in the endometrial epithelium that affects the adhesion of the blastocyst to the epithelial endometrial wall (Dominguez *et al.* 2010, Cha *et al.* 2012).

While not equal, there are microbial similarities between the oral and vaginal environments in the presence of both PD and BV, respectively (Genco 1992, Cauci 2004). This relationship may show common pathophysiology mechanisms, for instance, deficient host response to infection (Genco 1992, Cauci 2004, Pretorius *et al.* 2007). Yet, PD and BV may be related through the similarity in the microbiota, in particular, Prevotella species and via Prevotella-mediated

inflammation (Larsen 2017, Coyne *et al.* 2019). On the one hand, Prevotella stimulate the release of IL-1b, IL-6 and IL-23 by dendritic cells through Toll-like receptor 2 (TLR2), that mediates IL-17 production by T helper 17 (Th17) cells and in turn activate neutrophils (Larsen 2017). On the other hand, recently discovered peptide toxins secreted by Prevotella may play an important role, contributing to the widespread inflammation (Coyne *et al.* 2019). Consequently, Prevotella-mediated chronic inflammation leads to localized bone loss and tissue destruction in PD and endotoxemia via lipopolysaccharides. Local inflammation caused in both pathologies disseminates and may collapse systemic health (Larsen 2017).

Comprehensively, the hypotheses for contamination are the haematogenous spread or oral-genital direct transfer (Hill 1993, Edwards & Carne 1999, Harville *et al.* 2004); however, the relationship between these two pathologies remains poorly understood.

Hormonal dysregulation through chronic kidney disease

CKD is a general term for heterogeneous disorders affecting the kidney's function and structures (Levey & Coresh 2012, Ricardo *et al.* 2015, Webster *et al.* 2017). The discrepancy in disease expression is connected to etiology, progression rate and severity (Levey & Coresh 2012). Nowadays, the definition of CKD is based on the presence of kidney damage or decreased kidney function for 3 months or more, irrespective of clinical diagnosis (National Kidney Foundation 2002, Vassalotti *et al.* 2007), and it has been found that CKD is developed through chronic inflammation in the renal tissues (Chopra & Sivaraman 2019). The burden of early stages of CKD is difficult to measure because CKD is found mostly before the onset of symptoms (Stevens & Levey 2009), and its 10–15% worldwide prevalence continues to rise, particularly among female patients (Dumanski & Ahmed 2019, Elhoseny *et al.* 2019).

Among its vital roles, kidney is responsible for sex hormones turnover and its dysfunction directly influences the HPO axis, resulting in progressive fertility loss (Finkelstein *et al.* 2007, Kuczera *et al.* 2015, Ahmed & Ramesh 2016, Palmer & Clegg 2017, Dumanski & Ahmed 2019). Regarding this loss of fertility secondary to CKD, luteinizing hormone (LH) and the follicle-stimulating hormone (FSH) increase but the levels of estrogen and progesterone dwindle, culminating in an abnormal hormonal cycle (Dumanski & Ahmed 2019). Furthermore, CKD female patients may also experience anovulation, reduced ovarian reserves, menstrual disorders, abnormal endometrium, reduced libido, and sexual dysfunction (Kuczera *et al.* 2015, Palmer & Clegg 2017, Dumanski & Ahmed 2019). As a consequence, the rates of spontaneous pregnancy in CKD patients

decrease to 1–7%, rather than the physiological 65–94% (Hou 2007).

Remarkably, PD and CKD share a relationship based on bacterial spreading and cytokines dissemination from periodontal pockets through the bloodstream (Kshirsagar *et al.* 2007, Fisher *et al.* 2008, Chambrone *et al.* 2013, Ismail *et al.* 2015, Ricardo *et al.* 2015, Akram *et al.* 2016, Sharma *et al.* 2016, Almeida *et al.* 2017, Chopra & Sivaraman 2019, Deschamps-Lenhardt *et al.* 2019). Moreover, a recent systematic review concluded that patients with PD have a risk of 1.49–2.39 times higher to develop CKD, and this risk is directly related to the severity of periodontal destruction (Deschamps-Lenhardt *et al.* 2019). Notwithstanding, the PD treatment in CKD patients might partially recover kidney function through the reduction of the inflammatory state, in particular, improvement of glomerular filtration rate, creatinine levels, and endothelial function (Deschamps-Lenhardt *et al.* 2019).

Since CKD is one of the causes of female infertility, and PD is a well-established modifiable risk factor towards CKD, it is reasonable to consider that PD might worsen the women infertility secondary to CKD. Thus, it is important to consider periodontal screening in the multidisciplinary management of infertile women due to CKD, and future studies should investigate this possible association.

Age

Age is undoubtedly related to female fertility (Eijkemans *et al.* 2014), and the age at last birth (ALB) curve shows a gradual increase to 35 and 40 years old, and after that a rapidly increase in fertility woman's loss (Leridon 1977, Spira 1988, Wood 1989, Eijkemans *et al.* 2014). In addition to the latter, age is also a risk factor for onset and development of PD (van der Velden 1984, Rajendran *et al.* 2013, Ebersole *et al.* 2016). We find relevant to emphasize that the age peak of PD onset is placed at 38 years old (Kassebaum *et al.* 2014) (ranging 25–45 years of age) which may overlap the time interval of the major likelihood of conception. Further, women using hormonal contraceptives have higher association with PD (Tilakaratne *et al.* 2000, Mullally *et al.* 2007, Prachi *et al.* 2019). Therefore, the risk timeline for PD onset matches the timeline for pregnancy, and this factor should not be forgotten.

Assisted reproductive technologies

Many couples continue to be diagnosed with idiopathic infertility or receive descriptive diagnoses that do not provide a cause for their defect (Cousineau and Domar 2007, Ray *et al.* 2012, Djurovic *et al.* 2018), and therefore hampering their infertility problem (Matzuk & Lamb 2008). Besides, whether the etiology is known or

not, the advances in ART have overcome this problem, though ART is used to make it possible to conceive and is not a cure to the causes of infertility (Qin *et al.* 2017). However, females believe that fertility can be manipulated through ART (Te Velde *et al.* 2010), and many women believe erroneously that infertility care can address the fertility decline associated with age (Maheshwari *et al.* 2008).

ART range from a simple oral administration of drugs to stimulate ovulation, to more invasive techniques such as intrauterine insemination to install a processed sample of sperm into the uterine cavity directly, and IVF (Qin *et al.* 2017, Sullivan-Pyke *et al.* 2017).

Nowadays, 65 countries reported the use of ART during 2011, and Europe had the highest number of participants (41.6%), followed by Asia (33.9%) and North America (16%) (Adamson *et al.* 2018). Besides, evidence confirms that pregnancies resulting from IVF and/or intrauterine insemination have worse adverse perinatal outcomes than spontaneous conceptions, after controlling for patient factors (Hansen & Bower 2014). These outcomes include an risk of low birth weight, preterm birth, stillbirth, perinatal mortality, admission to a neonatal intensive care unit, antepartum haemorrhage, hypertensive disorders during pregnancy, gestational DM (Helmerhorst *et al.* 2004, Chung *et al.* 2006, McDonald *et al.* 2010, Pandey *et al.* 2012, Pinborg *et al.* 2013, Davies *et al.* 2017), and also congenital anomalies, imprinting disorders (Vermeiden & Bernardus 2013), autism spectrum disorders (Lehti *et al.* 2013) and neurodevelopmental disorders (Strömberg *et al.* 2002).

Despite the lower number of available literature, the stimulated ovulation via a hormonal overload in ART might turn women more prone to gingival inflammation (Haytaç *et al.* 2004, Vasudevan *et al.* 2013, Lalasa *et al.* 2014, Pavlatou 2014, Smadi 2017), warranting constant periodontal monitoring. Notwithstanding, PD may act as a modifiable risk factor limiting conception (Hart *et al.* 2012, Nwhator *et al.* 2014, Paju *et al.* 2017), and periodontal therapy on women prior to conception reduces significantly adverse birth outcomes (Jiang *et al.* 2013). Since PD is common among adults (Albandar & Rams 2002, Dye 2012, Petersen & Ogawa 2012) and there is a possible link between PD and pregnancy outcome (Wu *et al.* 2015, Abariga & Whitcomb 2016, Puertas *et al.* 2017) in a world where the infertility rates are high, highlighting its relation with infertility treatments becomes very relevant.

Overall, it should be noted that ART is not harmless (Zhu *et al.* 2006, Wisborg *et al.* 2010, Zollner & Dietl 2013, Morency *et al.* 2016, Iwashima *et al.* 2017). Therefore, it is crucial to investigate the real implication of PD in female infertility. Besides, if proven a negative impact of PD in women seeking ART, then periodontal consultations might be of importance for prenatal care, possibly increasing fertility success and avoiding complex and invasive treatment such as ART.

Conclusions

This comprehensive review has brought to light gaining evidence that links female infertility-related conditions as a modifiable risk factor towards PD. Further research is needed to clarify this causal relationship as well the mechanisms underlined. The current evidence does not support a role for PD in on female infertility-related conditions.

Declaration of interest

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V M, J B conceived and planned the review article. J L, M P, J B and V M have performed the review of the literature. J L, M P, J B, L P, J J M and V M drafted, provide critical feedback and helped shape the research and manuscript. J L and M P are equally first authors.

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