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Review Article
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Biomarkers of Female Infertility: Exposure, Effect and Chemical Modification of Biomolecules

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ABSTRACT: Female infertility is a health condition that affects the ability of woman to conceive over a period of continuous sexual intercourse. This condition has led to psychological and social anguish, anxiety, and depression resulting from hormonal impairment, disease infection, oxidative stress, xenobiotics, environmental pollutants, and other factors. Need to say, extensive studies on the biomarkers for female infertility are still in the developmental stage in reproductive medicine to unravel remedies based on improved technologies. In this review, we have reported some potential biomarkers responsible for female infertility, captured and documented recent biomarkers of effect in female infertility arising from exposures to diverse environmental toxicants and highlighted the progress in assisted reproduction technologies (ART) towards averting the societal consequences arising from female infertility.

Keywords: Female infertility, Biomarkers, Assisted reproduction technology, Reproductive medicine.

Introduction

The inability to reproduce after several attempts of unprotected copulation between a man and a woman is a reproductive health challenge called infertility. Infertility affects many couples that are within the age of procreation globally (Vander Borght and Wyns, 2018). Several factors such as environmental, lifestyle, disease infection and diet, could be responsible for infertility. Biomarkers are often referred to as quantifiable indicators of the presence of some disease conditions that can help to obtain information on the extent of a female's susceptibility towards the lethal impacts of exposure to several substances such as xenobiotics, e-waste, heavy metals, pesticides, herbicides, air pollutants, flame retardants, etc. (Palmer and Barnhart, 2013; Wahid *et al.*, 2017). Several biomarkers for specific roles in the human body have been identified in reproductive medicine, including biomarkers of: diseases at different stages of development, effect on the biological functions, exposure to different environmental contaminants, and susceptibility-encompassing epigenetic biomarkers (Wahid *et al.*, 2017). Over the years, many reproductive biomarkers dealing with prognosis of females' infertility- associated conditions such as placental-mediated and fetal health complications (Manokhina *et al.*, 2017), ovarian reserve (Steiner *et al.*, 2017), tubal factor infertility (TFI) due to genital chlamydia infection (Palmer and Barnhart, 2013) amongst others, have been identified. In this review, recent biomarkers of female infertility arising from environmental exposures to diverse toxicants were identified and discussed. Also, the progress in alternative reproduction procedures based on assisted reproduction technologies (ART) was also highlighted.

Early markers of female infertility

Numerous pathologic processes are associated with infertility and their systemic effects may give rise to chronic morbidity and serious future events (Senapati, 2018). The most common symptom of female infertility is the inability to conceive. However, too long or too short menstrual cycle and ovulation disorder are frequently identified as warning signs (Mayo Clinics, 2019).

The prevalent causes of infertility in females include polycystic ovary syndrome (PCOS), endometriosis, hypothalamic dysfunction, fibroids, too much prolactin, and diminished ovarian reserve. These lead to disruptions in reproductive pathways and may be an implication for future medical conditions (Dumesic *et al.* 2015; Randeva *et al*., 2012).

PCOS is a hormonal disorder that makes the female ovaries very large with small cysts on the outer edges. This syndrome is predominant in women and can be aggravated by certain deficiencies. Kyei *et al*. (2020) showed that Vitamin D deficiency and oxidative stress (OS) can cause low-grade inflammation towards worsening the pathophysiology of PCOS. However, the combination of MitoQ10 and Vitamin D3 meaningfully lowered the levels and expression of estradiol, progesterone, other enzymatic antioxidants, and mRNAs of 3β-HSD, HO-1, Cyp19a1, StAR, Nrf2, Keap1, and Cyp11a1. In another study, Akino *et al*. (2018) studied the functions of Nrf2 and Keap1 in ovarian granulosa cells (GCs) by subjecting human ovarian tissues to immunohistochemistry. Activation of Nrf2 could assuage oxidative stress in GCs, thereby averting infertility in females. Xu *et al*. (2015) presented data suggesting that in the pathophysiological of PCOS, miRNAs and the targeted pathways (e.g. Notch signaling pathway), however, Notch3 and MAPK3 were proven to be controlled by miR-483-5p. Meanwhile, Alam *et al*. (2020) examined the discrepancy in SIRT1 (anti-oxidants) and cortisol (pro-oxidants) levels of fertile and infertility females depicted by a strong negative association observed between both markers ($r=0.244$, $p<0.001$), however, SIRT1 and cortisol were substantially reduced in the infertile females than the fertile ones, respectively. By exploring information on the significance of IL-6 in reproductive physiology, Benjamin *et al*. (2020) evaluated and deduced thatIL-6-174 G/C polymorphism can be considered as a possible genetic marker for PCOS but not for endometriosis and tubal damage disorders. Similarly, Alves *et al*. (2020) examined the association between GSTM1 and GSTT1 gene polymorphisms with PCOS in infertile women. The study asserted that carriers of the GSTT1 null genotype have a higher predisposition to PCOS and other causes of infertility, while GSTM1 null genotype is solitarily connected with all causes of infertility when GSTT1 is null. More so, da Silva *et al*. (2020) proposed that for women with early and advanced endometriosis (EI/II and EIII/IV, respectively), dysregulation of miR-532-3p may be a possible mechanism in the pathogenesis of endometriosis-related infertility, however, genes regulated by this miRNA are associated in significant pathways towards attaining oocyte competence. In a non-human study, Kapoor *et al*. (2019) observed that the medicinal plant, Naringenin, possess anti-endometriotic therapeutic potential by improving the expression of prognostic markers (TAK1, PAK1, VEGF, and PCNA) playing vital roles in the advancement of endometriotic cells in the rat. In the same vein, Samare-Najaf *et al*. (2020) demonstrated the quercetin and vitamin E can synergistically alleviate doxorubicin-induced toxicity in the ovary and uterus, and the secondary bone-related effects in a rat model.

Biomarkers of female infertility

There are several plausible biomarkers responsible for reproductive impairment and are in different developmental stages. They serve as the primary early-warning indicators resulting from the impact of the environment which requires comprehensive authentication and characterization in an ecosystem. Many available reproductive biomarkers are designed specifically for the diagnosis of PCOS, endometriosis, infertility, and the feasibility and site of early pregnancy (Wahid *et al*., 2017). For example, multivariate biomarkers such as Anti-Müllerian hormone (AMH) have been demonstrated as a delicate biomarker that facilitates transition into menopause at low levels (Kaori *et al*., 2013). Thus, an AMH assay can become an indirect biomarker for women who are at risk of premature ovarian failure or PCOS (Dewailly and Laven, 2019). Also, Gat *et al.* (2017) established a link between AMH in the serum and the proportion of euploid embryos because of the strong domination of ≤ the 36 age group in the subpopulation of infertile couples.

Furthermore, the studies of Lai *et al*. (2014) observed that hypermethylation of AJAP1, HS3ST2, and SOX1 is a biomarker for endometrial carcinoma in females suffering from atypical hyperplasia. Also, Hanson *et al*. (2020) reported that the telomere length of white blood cells which is short is linked to the high rates of aneuploidy prevalent in infertile females undertaking *in-vitro* fertilization. For spouses with idiopathic infertility, Laanani *et al*. (2018) showed that buccal micronucleus cytome assay is a suitable biomarker and a minimally invasive cytogenetic method for evaluating genomic damage.

Exposure to toxicants and biomarkers of female infertility

Biomarkers are often used as a tool to determine the extent and potential health risks associated with exposure measurements and health effects that occurred within a given time frame. However, the exposure assessment investigates the concentration of a chemical substance in the biota (Brucker *et al*., 2020). Generally, most of these chemical compounds/substances in the environment are chemicals that affect the hormonal-dependent pathways responsible for the development of gonad, via direct interaction with hormone receptors or epigenetic and cell-cycle regulatory modes of action (Sifakis *et al*., 2017). Table 1 summarizes the outcomes from the assessment of different biomarkers of exposure over a given period of time.

Xenobiotics, microplastics, and biomarkers of female infertility: Numerous studies have examined the effects of compounds such as phthalates, bisphenols (BPA), which are endocrine disruptors (ED) and microplastics on human health using urinary metabolites. The perinatal exposure to BPA renders some lethal effects such as the hypothalamic-pituitary-ovarian axis dysregulation in pups and adults, with a advanced maturation of the axis through damage of GnRH pulsatility, gonadotropin signaling, and sex steroid hormone production (Pivonello *et al*., 2020). Also, BPA exposure may cause development of PCOS-like abnormalities via impairing sex hormones secretion that affect ovarian morphology and functions, particularly follicle loss (Hart, 2016; Matuszczak *et al*., 2019; Pivonello *et al*., 2020).

Out of 805 urine samples randomly collected, ED were detected in more than 90% of the samples (Faÿs *et al*., 2020). Machtinger *et al*. (2018) observed that there is no connection between the concentration of urinary phthalate metabolite and reduced probability implantation, pregnancy, or live birth of the 136 women that have undertaken in vitro fertilization (IVF). The findings of Watkins *et al*. (2017) proposed the vulnerability of the female reproductive development to the effects of exposure to phthalate or BPA at dangerous periods of in-utero development. More so, Teh *et al*. (2019) conducted a case series of infertility on young women exposure to antiretroviral drugs owing to perinatally acquired HIV. The study shows that the overall reproductive health status of the participants was comparable to the general population.

Furthermore, the exposure of humans (via inhalation, ingestion, or contact) to microplastics is widely evident. However, only a minute fraction (<20 μm) can find its way into the internal organs, while smaller fractions (∼10 μm) can penetrate all organs and cell membranes, and pave through the blood-brain barriers and placenta. Although the information on the detrimental effect of microplastics on female fertility is scanty, their potential effects may attribute to their physicochemical properties (such as size, shape, presence of additives and polymer type), concentration, microbial biofilm growth. Also, no straightforward mechanism of their actions has been put forward so far, but, hydrophobic interactions, variation in pH, particles age, and composition of polymer are most likely to occur (Campanale *et al*., 2020). In a study on the reproductive toxicity of polystyrene microplastic (PS-MP) on the ovary of rat samples, oxidative stress was elicited and was characterized by decreased activity of glutathione peroxidase, catalase, and superoxide dismutase while the level of malondialdehyde increased (Hou *et al*., 2021). In addition, PS-MP was reported to cause fibrosis via activation of Wnt/β-Catenin signaling pathway and apoptosis of granulosa cells of ovary via oxidative stress generation, both of which ultimately lead to decreased ovarian reserve capacity (An *et al*., 2021).

Heavy metals and biomarkers of female infertility: Heavy metals are ubiquitous in different aspects of the ecosystem and they are well known to be a prominent toxin in female reproductive tracts (Tchounwou *et al*., 2012). The deterioration of the environment via the leakage of certain toxic trace metals can lead to the increased risk of human health challenges including reproduction concerns (Rzymski *et al*., 2015). As such, prolonged heavy metals exposure has been demonstrated to affect menstrual cycles, reduced gestational weight, delayed conception time, alter the production of hormones, premature birth, and miscarriages (Kumar, 2018; Lee *et al*., 2020) and plausible cause infertility issues in women (Lei *et al*., 2015). Generally, the mechanism of heavy metal-induced toxicity is based on the generation of reactive oxygen species, thereby causing oxidative damage and health-related adverse effects (Rehman *et al*., 2018). Also, these heavy metals essentially react with compounds such as chloride and oxygen in the body to execute their toxic effects (Rusyniak *et al*., 2010). For instance, the ingestion of Cd into the blood allows its transport by proteins such as albumin and metallothionein (MT) in a bound form. Cd can be preserved in the kidney and can lead to tubular necrosis. In some experimental investigations, Cd toxicity has a perturbed effect the level of enzymes that maintains oxidation-reduction reactions. More so, Cd can circuitously induce oxidative stress, thereby hindering their normal functions of oxidative enzyme (Olaolu, 2018).

The findings of Bloom *et al*. 2011 show that there is no association between blood heavy metal and fecundity, but exposure to Mg and Zn may influence female fertility in varying directions. Similarly, Salih and Jaafar (2013)confirmed that Fe, Mg, and Zn may impact female fecundity as well as elevated levels of Fe, Mg, Pb, and Zn in the blood and samples which may result in fertility issues in females. However, the systemic review of Pollack *et al*. (2014) suggests a possible connection between cadmium and preeclampsia and some conflicting pieces of evidence for fertility-related consequences.

Table 1: Summary of the outcomes from the assessment of different biomarkers of exposure over a given period of time

Sample Population	Biomarker of Exposure	Comparators	Biological Sample	Outcome	Period	Reference
Heavy Metals						
124 participants	Pb and Cd	Pregnant and Infertile women	Blood	A significant association between low level of Pb and Cd in the blood and infertility which could affect reproductive health.	2013-2016	(Lee *et al*., 2020)
1796 participants	Hg	Total blood mercury and infertility	Blood	No significant association exists between the comparators based on a fully-adjusted model.	2013-2016	(Zhu *et al*., 2020)
732 women	Hg	Pregnant women	Diurnal cortisol	No main effects of Hg or psychosocial stress exposure on diurnal cortisol.	6 months	(Schreier *et al*., 2015)
59 preclamptics, 150 normal pregnant, and 122 non pregnant women	Pb, Ca and P		Blood	The increase in blood Pb, with parallels, decrease in serum Ca andP, may cause the development and progression of preeclampsia.		(Ikechukwu *et al*., 2012)
20 to 40 years old women	Pb, Zn, As, Mg, Co, Sn, Ag, Sb, Fe, Cr	Women with infertility and weakness fertility	Blood and Urine	Fe, Mg and Zn may impact female fecundity. Also, Fe, Mg and Zn caucus a different affect in the blood and urine samples.		(Salih and Jaafar, 2013)
Others						
600 women	Atmospheric pollutants		Antral follicle	Every 10mg/m^3increase in SO_2concentration level during the entire development stage of antral follicle was associated with a -0.01 change in AFC (95% confidence interval.	2013-2016, 2017-2019	(Feng *et al*., 2021)
317 women	Triclosan	Urinary triclosan (UT) and serum thyroid function (STF)	Urine and serum	There was an inverse association between UT concentrations and precise STF biomarkers.		(Skarha *et al*., 2019)
6621 cycles of 4581 patients	PM_{10}, NO_2, CO, SO_2, andO_3		IVF cycle data	There was a connection between the high ambient level of the air pollutants and reduced probabilities for reaching intrauterine pregnancy using multiple IVF cycle data.	2006-2014	(Choe *et al*., 2018)
1077 pregnant French women	Pyrethroids		Urine	The urinary levels of pyrethroid metabolites were positively correlated to inappropriate lifestyle, domestic pesticide use, and living in the vicinity of crops during pregnancy.	2011	(Dereumeaux *et al*., 2018)

Sample Population	Biomarker of Exposure	Comparators	Biological Sample	Outcome	Period	Reference
211 women	OPCs	Infertile women	Urine	Exposure to OPCs in flame retardants may be one of many risk factors for lower reproductive success.		(Rapaport, 2017)
116,430 female nurses	($PM_{2.5-10}$)		Nurses' health data	There was an association between all size fractions of PM exposure, traffic-related air pollution, and infertility prevalence.	1989-2003	(Mahalingaiah *et al*., 2016)
1000 women	PM, NO_2, and NO_x		Land use regression modeling	There was an association between reduced fertility rates due to high traffic-linked air pollution.	2011-2012	(Nieuwenhuijsen *et al*., 2014)
304 men and 300 women	Organochlorine pesticides (OCPs)		Serum	OCPs can cause anti-androgenic and estrogenic effects in men and women respectively.		(Freire *et al*., 2014)
Female rats	Cypermethrin		Ovarian weight	Degenerative changes in ovary due to high follicular atresia and decreased concentration of proteins lipids and cholesterol.	4 weeks	(Sangha *et al*., 2013)
Women's Risk of Endometriosis	OCPs		Serum	Serum level of β-HCH and mirex were positively linked with endometriosis.	1996-2001	(Upson *et al*., 2013)
15 women seeking fertility treatment and 21 pregnant women	OCPs	Fertile and infertile women	Questionnaire	Exposure to OCPs (*p,p'*DDE) may heavily influence female fertility.		(Bastos *et al*., 2013)
53 infertile couples	Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA		Human peripheral blood mononuclear cell	PFOS and PFOA concentrations overlapping the limit of detection of 0.5 ng/g wet weight (ww).		(La Rocca *et al*., 2012)
Pregnant Wistar rats	Diisononyl phthalate (DINP)	Reproduction and sexually dimorphic behavior	Fetal	DINP causes anti-androgenic effects on reproductive development.		(Boberg *et al*., 2011)
1,227 women	Phthalate metabolites	Endometriosis and uterine leiomyomata	Urine	There was a positive association for monobutyl phthalate and inverse associations for mono (2-ethylhexyl) phthalate in relation to endometriosis and leiomyomata with 7 and 12 % respectively.	1999-2004	(Weuve *et al*., 2010)

Pesticides, herbicides, insecticides, and biomarkers of female infertility: Pesticides, insecticides, and herbicides are widely used for agricultural purposes to control pests, weeds, and insects respectively both in the farmland and surrounding residential area. These substances are usually produced from harmful and toxic chemical compounds that have a long-term effect on human health after prolong exposure. For example, exposure to high dose atrazine is linked to delay vaginal opening leading to delayed puberty and reduced body weight in female rat studies (Davis *et al*., 2011). Also, exposure to synthetic chemical compounds like organochlorines, organophosphates, carbamates, pyrethroids, and triazines can lead to disturbances in female reproductive functions, thereby resulting in subfertility, infertility, estrous malfunctioning, anovulation, and early reproductive senescence (Rattan *et al*., 2017).

There are numerous plausible mechanisms associated with pesticide/herbicide/insecticide-mediated toxicity in humans. However, the most prevalent are oxidative stress and/or receptor-mediated mechanisms. Besides, the inflammatory and anomalous epigenetic mechanisms associated with the exposure to these toxicants are still evolving (Alavanja *et al*., 2013). The prolonged exposure to these toxicants leads to the production of ROS (superoxides) whose consequential excessive production can cause the damage of the cell's DNA and protein. According to Alavanja *et al*. (2013), the oxidation of a pesticide catalyzed by cytochrome P450 (CYP) which could subsequently lead to the formation of a hydroxylated metabolite and give rise to the uncoupling reactions and the formation of superoxide (O_2). More so, the production of metabolites of pesticides, such as compounds of quinones or bipyridinium undergoing redox cycling can also produce superoxides. Furthermore, overwhelming superoxide flux can be generated in the reactions of the mitochondrial electron transport chain processes. Meanwhile, the activation of NADPH oxidase by pesticides can release superoxide radicals (Alavanja *et al*., 2013; Choi *et al*., 2010).

The oral exposure to simazine causes anogenital distance, decreased ovarian and uterine weights as well as amplified apoptotic granulosa cells in the ovaries of female offspring in mouse samples (Park *et al*., 2014). Studies have also shown that the long-standing health effects of prenatal exposures to glyphosates and paraquat could affect the reproductive system and the fetus of pregnant women (Kongtip *et al*., 2017; Vandenberg *et al*., 2017). Barkoski *et al*. (2018) detected urinary pesticide metabolites in ≥93% of pregnant specimens analyzed which could be a detrimental challenge for exposure assessment. However, Chiu *et al*. (2018) observed that the ingestion of high-pesticide residues from vegetables and fruits was linked with the low likelihood of pregnancy and live birth after the infertility treatment of 325 women with ART. More so, a study on the blending of different pesticide compositions was found to hinder the reproductive system of female rats (Pascotto *et al*., 2015). Meanwhile, the results from the AMH concentrations in relation to pesticides and indoor air pollution conducted by Whitworth *et al*. (2015) are indicative of decreased ovarian reserve associated with exposure to pyrethroid pesticides. In another study, the exposure-response association and modifier effect of ambient exposure to polychlorinated biphenyl-153 and dichlorodiphenyldichloroethylene (*p,p'*-DDE) may have effect on fetal growth (Casas *et al*., 2015).

Flame retardants, e-waste, and biomarkers of female infertility: Flame retardants are synthetic chemical compounds that have gained attention in upholstered furniture, electronics devices (a major constituent of e-waste), and plasticizers, e.t.c. (Mendelsohn *et al*., 2016). Basically, these consumer goods products are prepared with organophosphate compounds (OPCs), replacing polybrominated biphenyls (PBDE) to meet flammability requirements. These compounds gets released into the environment gradually since they are not covalently bound to the materials in the product (Chupeau *et al*., 2020). Metabolites of OPCs which can be used as biomarker have been spotted in the urine and urinary tracts of mothers and children (Butt *et al*., 2014, 2016; Saillenfait *et al*., 2018). Consequently, exposure to OPCs and their corresponding metabolites is directly associated with a endocrine-disrupting effect on pregnancy loss or reproduction impairment in women (Messerlian *et al*., 2018). Liu *et al*. (2013) observed that exposure to triphenyl phosphate (TPP) and Tris (1,3-dichloro-2-propyl) phosphate (TDCPP) disrupts the sex steroid hormone balance, GnRH, GtHsgenes, and plasma vitellogenin levels, which could affect reproductive performance in zebrafish. Similarly, Wang *et al*. (2015) showed that developmental exposure to a low concentration of TDCPP has endocrine disruption, estrogenic activity, as well as reproductive effects on zebrafish samples. More so, the observed phenotypic responses to the exposure of Tris (1-chloro-2-propyl) phosphate (TCPP) and TDCPP may be connected with perturbation of the thyroid hormone pathways, critical for normal growth and development in birds (Farhat *et al*., 2013). Nevertheless, some studies have shown that metabolites of some concentrations of urinary OPCs were negatively related to proportions of successful fertilization, clinical pregnancy, implantation, and live birth after using IVF (Carignan *et al*. 2018; Hu *et al*., 2020). Additionally, Zhang *et al*. (2016) reported the level of BPA compounds in the urine of people living in and around e-waste dismantling facilities in China and observed the presence of 8-hydroxy-2'- deoxyguanosine (8-OHdG), a marker of oxidative stress. The lipid-adjusted concentrations of PBDEs and OH-BDEs of 189 couples show a higher distribution of the contaminants in females than in male partners.

Air pollutants and biomarkers of female infertility: The health implications of exposure to air pollutants have been studied widely with evidence showing a consistent association between exposure to ambient concentrations and high rates of pregnancy complications, preterm delivery, and low birth weight, and fertility challenges amongst others (Lee *et al*., 2013; Fleischer *et al*., 2014; Nieuwenhuijsen *et al*., 2014). Human activities such as heavy traffic, combustion of fossil fuels, and industrial activities are the major route of the release of toxic contaminants (e.g., poisonous gases, volatile organic solvents, heavy metals and particulate matter, PM) into the air. Need to say, the chief human exposure routes are via ingestion (contaminated food and water) and inhalation (toxic gases and PM) (Conforti *et al*., 2018). Recent studies have demonstrated that PM can amass in the reproductive organs and barriers protecting reproductive tissues, thereby disrupting hormone levels, ultimately affecting fertility (Wang *et al*., 2021). Quraishi *et al*. (2019) showed that prolonged exposure to PM and NO_2 caused plausible synergistic effects of air pollution and diminished ovarian reserve on fertility and live birth. In addition, the report of Carré *et al*. (2017) reported that the quality of air has a great impact on the health and reproductive function, supported epidemiological studies on the defects during gametogenesis in populations exposed to air pollutants in human and animals.

Biomarkers of effect

Biomarker of effect is used in the assessment of health risk the effect of a chemical on a physiological process. Different biomarkers of effect including oxidative stress (OS), cytokines, hormones, inflammatory, immunological markers have been studied and reported to detect several changes in the female reproductive system. The reported outcomes from the assessment of some biomarkers of effect are summarized in Table 2.

Oxidative stress (OS): Oxidative stress (OS) is a state of imbalance between prooxidants and antioxidants usually caused by amplified levels of reactive nitrogen or oxygen species (RNS or ROS), or by reduction of antioxidant defense mechanisms (Burton and Jauniaux 2011). The excess production of ROS can suppress the antioxidant defense mechanisms, giving rise to unsuitable conditions for normal physiological reactions (Tošić-Pajić *et al*., 2017). In most cases, this imbalance is linked with the pathophysiology of many reproductive diseases such as TFI, POCS, endometriosis, placental disorders, inexplicable infertility as well as pregnancy complications like miscarriage, repeated pregnancy losses, and preeclampsia (Agarwal *et al*., 2012; Pereira and Martel, 2014).

Nsonwu- Anyanwu *et al*. (2015) asserted that oxidative DNA damage and the reduction in the antioxidant capacity may cause Chlamydia-induced tubal damage which is associated with tubal infertility. Meanwhile, investigations into the urinary levels of OS suggests that a non-linear association, thus, environmental chemicals are associated with adverse reproductive damage through generation of oxidative stress (Rosen *et al*., 2019).

There is a series of the complex mechanism that involves the transition of post-ovulatory oocytes to apoptosis, all of which are motivated by a rise in OS level. The oxidative occurrence of zone pellucida hardening is catalyzed by an ovoperoxidaze found in cortical granules and can be released by an exocytotic process from the surface of the oocyte. Although the mechanistic pathways involving the generation of OS within the female germ line are unknown, the oocytes possess NADPH oxidase (NOX_2) and lipoxygenase. Nevertheless, irrespective of the origins free radical in the cell, the dismutative formation of hydrogen peroxide gives positive outcomes in zona hardening and oocyte maturation, while lipid aldehydes such as 4-HNE are considered as an important mediator of pathological change. Similarly, negative outcomes (viz-a-viz weakened functionality, senescence and damage to DNA and chromosome segregation) are generated due to excess ROS (Kala *et al*., 2017).

Additionally, OS have been discovered in the follicular fluid of IVF/embryo transfer (ET) patients (Attaran *et al*., 2000; Pasqualotto *et al*. 2004; Oyawoye *et al*. 2003; Paszkowski *et al*., 2002). Van and his colleagues established poorly vascularised follicles and low intrafollicular oxygenation has been related to decreased oocyte developmental capacity, demonstrated by an increase in the incidence of cytoplasmic defects, and irregular chromosomal segregation (Van *et al*., 1997; Yang *et al*., 1998). As a result, increased OS levels are detrimental to embryo growth and development.

Cytokines: Cytokines are fashioned by many cell types including endometriotic tissues, and they perform various roles in the pathogenesis of endometriosis and endometriosis-associated infertility, modulates the immune system, and contribute to the regulation of the ovarian cycle (Sarapik *et al*., 2012). Al Jameil *et al*. (2018) uncovered that interferon-γ (a cytokine) is strongly linked with LH and prolactin in women with frequent pregnancy miscarriage. The evaluation of cytokines from 210 patients showed limited potential of cytokines for diagnosis of endometriosis in the plasma of the subjects (Knific *et al*., 2019).

Table 2: Reported outcomes from the assessment of some biomarkers of effect

Sample population	Biomarker of effect	Comparators	Biological sample	Outcome	Reference
Human study					
Women with endometriosis	Uranium	Cytokines and chemokines	Serum	Uranium exposure alone was associated with an increase in inflammatory chemokines. Most of the elevated chemokines in endometriosis cases are vital in attracting T helper-2 cells, which may be crucial towards understanding the immune response in endometriosis.	(Greene *et al*., 2019)
66 infertile women with Stage III or IV endometriosis	Dienogest (DNG)	-	Follicular fluids	The administration of DNG treatment before IVF-embryo transfer did not improve the clinical outcomes for infertile women with endometriosis.	(Tamura *et al*., 2019)
91 infertile women related to Endometriosis	Vitamin C and E, malondialdehyde, and superoxide dismutase	-	Plasma and follicular fluid	Infertile women with endometriosis showed a low level of antioxidant capacity.	(Prieto *et al*., 2012)
63 infertile women	Paraoxonase-1 (PON-1)	Relationships between OS, PON-1, and MCP-1 in women	Serum	Elevated serum oxidative stress was significantly correlated with an increase in serum PON-1 activity and without any evidence of a proinflammatory reaction.	(Marsillach *et al*., 2010)
Animal study					
80 female rats	Chronic stress of exposure to cold-water immersion for 15 mindaily for 30 days.	Hormones that control female reproduction	Vaginal smears	Chronically stressed females exhibited disrupted estrous cyclicity, decreased receptivity, low pregnancy rates, and lower numbers of fetuses.	(Retana-Márquez *et al*., 2020)
Murine Ovarian endometriosis (OE) model	Iron catalyzed OS	-	Uterine tissue	Iron accumulation increased in the OE group, leading to OS in each stage of the follicles	(Hayashi *et al*., 2020)
Sprague-Dawley rats	Cholestasis	-	Blood	Cholestasis-associated reproductive toxicity in the rat model is restrictedly coupled with severe OS and mitochondrial impairment.	(Ommati *et al*., 2019)
Female Wister rats	4-Vinylcyclohexene diepoxide (VCD)	-	Oral administration	VCD-induced reproductive toxicity in female rats via oxidative damage, inflammation, apoptosis and hormonal disruption.	(Abolaji *et al*., 2016)

Sample population	Biomarker of effect	Comparators	Biological sample	Outcome	Reference
Sprague-Dawley female rats	Cyclooxygenases (COXs)	-	Uteri	COX-1 and COX-2 could be differentially regulated by steroid hormones and might be the key factors involved in embryo implantation, decidualization, decidua basalis regression and parturition in rats.	(St-Louis *et al*., 2010)
Immature female rats	Nitric oxide, NO	-	Freshly ovulated eggs	NO signals the accumulation of phosphorylated Cdk1 and induces postovulatory aging-induced abortive spontaneous egg activation in the rat.	(Premkumar and Chaube, 2015)
28 rats	VCD	-	Ovarian follicles	Administration of VCD to induce ovarian failure results in endocrine and anxiety-related changes that are similar to the symptoms exhibited by women during menopause transition.	(Reis *et al*., 2014)
32 female Wistar rats	2,5-Hexanedione (2,5-HD)	-	Ovary and uterus	2,5-HD exposure causes the disruption of hormonal homeostasis and induces OS in the ovary and uterus of rats; and may have toxicological implications in women occupationally exposed to *n*-hexane and methyl-*n*-butyl ketone.	(Abolaji *et al*., 2015)
Female Siberian hamsters	VCD	-	Ovarian follicles	Primordial follicle numbers were significantly reduced by VCD under both day lengths, and reproductive quiescence in short days did not appear to render the ovaries less susceptible to VCD-induced follicle depletion.	(Roosa *et al*., 2015)

Inflammation: Inflammatory disorders are also responsible for several gynecologic diseases affecting females of reproductive age. They are considered as a type of nonspecific immune response, either acute or chronic that affecting the trophoblast and trophoblast-endometrial interaction (Galland, 2010; Valin and Pablos, 2015). However, consuming more pro-inflammatory diets increased rate of abortion than consuming anti-inflammatory diet (Vahid *et al*., 2017). More so, the findings of the food record diary of 144 women undergoing fresh IVF cycles show that serum hypersensitivity C-reactive protein, IL-6 concentration and dietary inflammatory index are not predictive markers of outcomes (Diba-Bagtash *et al*., 2021).

Ovulation, menstruation, implantation, initiation of labor, and parturition and other female reproductive activities shows inflammation-related signs and symptoms (Goswami *et al*., 2008). These events may be linked to an increase in the expression of different inflammatory mediators, such as cytokines and growth factor which impact the immune and vascular compartments development and function (Goswami *et al*,. 2008; Serhan *et al*., 2008).

Inflammation also plays an important role in the pathogenesis of endometriosis, a disease characterized by increased expression of inflammatory factors and angiogenesis (Marki *et al*., 2017; Lagana *et al*., 2017). These leads to increased estrogen production, and causes the activation of both NF-kB and cyclooxygenase-2 (COX-2) leading to elevation in the level of prostaglandins (PGs) (Sugino *et al*., 2004). COX-2 levels are usually elevated in ectopic endometrioid implants. Proinflammatory cytokines, such as interleukine-1 (IL-1,6), can increase mRNA stability and COX-2 promoter activity in ectopic endometriotic stromal cells. According to Lagana *et al*. (2019), COX-2 and COX-2-derived PGE2 production were found to be higher in ectopic implants. However, inhibiting COX-2 was found to reduce epithelial and stromal cell invasion in endometriosis (Banu *et al*., 2008).

Immunology: Immunological infertility is the presence of an anti-sperm immune reaction capable of interfering with fertility variables (Dondero *et al*., 2011). Reproductive autoimmunity is related to reproductive immune cells been activated against self-reproductive cell, specifically reproductive immune cells activation directed against ovarian antigens (Haller-Kikkatalo *et al*., 2012). Fu *et al*. (2016) considered spermatogenic glyceraldehyde-3-phosphate dehydrogenase as a candidate biomarker of immune infertility and noticed a statistically significantly lower concentration of antibodies in the sera of infertile women.

Likewise, helper T-cells (Th), IL-17A, and IL-4 are other immunological factors implicated in the production of endometriosis, as revealed by Osuga *et al*. (2016). According to the researchers, endometriotic tissues showed higher levels of Th2 and Th17 cells. Furthermore, mixing IL-17A with TNF increases the secretion of IL-8 and CCL-20, implying that inflammation and the immune cells work together. These molecules may be possible biomarkers for disease progression.

Epigenetics and biomarkers of female infertility

Epigenetics studies the heritable changes in occur in expression of gene that do not include variations to the primary DNA sequence - a change in phenotype without a change in genotype - which in turn affects how cells read the genes (Bisht *et al*., 2019). Mice infertility has been traced to over 200 genes, however, most of the causative genes responsible for human fertility remain unidentified. The completion of the genomic sequencing project and the hap map project can assist the identification of effective genes in fertility since most infertility concern arises from complex diseases (Pouresmaeili, 2019). Nevertheless, both human and animal studies indicate that environmental exposures at early life either intrauterine or postnatal life can strongly impact the risk for adult disease and influence the health of their offspring, thus initiating a cycle of disease risk across many generations (Sales *et al*., 2017).

The unusual mechanisms of epigenetics play a crucial part in the pathogenesis of infertility and have unlocked novel avenues in establishing causes of infertility with its associated clinical manifestations (Abur and Gunes, 2021). Epigenetic regulation by DNA methylation mechanism enables the determination of the groups of genes that is switched on under a cellular condition. Also, epigenetic reprogramming at the developmental stage of the embryo is important in determining the fate of each differentiating cell (Messerschmidt *et al*., 2014).

The gene-environment interaction has crucial impacts in determining the epigenome and quality of the oocyte, which inspires female fertility (Bisht *et al*., 2019). Blasco *et al*. (2020) confirmed that the atypical level of some gene expression in granulosa cells might be involved in decreased fertility connected maternal aging, endometriosis, and low ovarian response. Besides, Olsen *et al*. (2020) showed that in the leukocyte epigenetic profile of women with diminished ovarian reserve, the somatic cells of human ovarian follicles have a distinctive epigenetic profile and a high frequency of epimutations suggesting premature aging.

MicroRNA: MicroRNAs (miRNAs) are single-stranded, small non-coding RNA molecules that contribute to post-transcriptional regulation by binding directly to messenger RNA targets, causing destabilization or translation

repression (Bartel *et al*., 2004). They regulate several biological processes in reproduction, including follicular cell proliferation and apoptosis, steroidogenesis and oocyte maturation (Assou *et al*., 2013; Sang *et al*., 2013; Xu *et al*., 2011). Studies have established that miRNA can be quantified in biological fluids and therefore, can signify prospective biomarkers (Liang *et al*., 2014; Wang *et al*., 2014; Traver *et al*., 2014).

miRNAs epigenetic regulation is a key element in development of endometriosis since the expression of miRNAs differs from the normal endometrium (Teague *et al*., 2010; Hawkins *et al*., 2011; Nothnick *et al*., 2019). Dysregulation of miRNAs of three family members: miR-200a, miR-200b and miR-141 has been reported to be involved in endometriosis progression (Teague *et al*., 2010). Likewise, it was shown that miR-20a targets TGF-β and Il-8 and their decrease is usually associated with increased proinflammatory molecular concentrations (Zho *et al*., 2014). This molecule also aims at $CLIC_4$ and VCL, leading to uncontrolled infiltration in endometrial cells (Wang *et al*., 2013).

miRNAs participate in the regulation of steroidogenesis in ovarian follicles as ovarian reserve status biomarkers (Hossain *et al*., 2012; Hu *et al*., 2013). Studies have demonstrated that miRNA expression in serum or follicular fluid samples is altered in women with PCOS syndrome (Ding *et al*., 2015; Sorensen *et al*., 2014; Long *et al*., 2014; Roth *et al*., 2014,). Furthermore, miRNAs play a crucial role in oocyte and embryo development (Xiao *et al*., 2014, Hossain *et al*., 2012) and one recent study linked miR-320a expression in FF to embryo quality (Feng *et al*., 2015). Scalici *et al*. (2016) screened 91 women with normal ovarian reserve and 30 women with PCOS having expression profiles of circulating miRNAs (let-7b, miR-29a, miR-30a, miR-140, and miR-320a) in human follicular fluid for their potentials to predict IVF outcomes. According to their findings, human follicular fluid having low number of mature oocytes (<2) had significant low levels of miR-320a compared with higher number of mature oocytes (>2). Furthermore, let-7b and miR-140 expression level is significantly downregulated, while miR-30a is up-regulated in FF samples from PCOS patients. The downregulated let-7b expression of FF in PCOS patients may be a reflection of abnormal folliculogenesis. Certainly, let-7b is implicated in the development of ovarian follicles (Cao *et al*., 2015, Zhang *et al*., 2013). Irregular estrogen receptor (ER) expression can also play a role in follicular development and ovulatory failure in females with PCOS (Jakimiuk *et al*., 2002). During embryo implantation, the highly expressed MiR-29a in the rat uterus is controlled by blastocyst activation and uterine decidualization (Xia *et al*., 2014).

*DNA Methylation*L DNA methylation is the transfer of a methyl group to the C-5 position of the cytosine base of DNA catalyzed by DNA methyltransferases (DNMTs) thereby resulting to modification of the function of the genes and gene expression (Jin *et al*., 2011). DNA plays key role in gene expression control through altering chromosomal structure, X chromosome inactivation, gametogenesis, DNA conformation, genomic imprinting, endogenous retrovirus silencing, DNA stability and the function way between DNA and protein (Sumei and Wanyin, 2018, Senner, 2011). The expression pattern of gene with DNA methylation is different in infertile tissue such as in endometriotic tissue compared to normal tissue. The endometrial DNA methylation patterns in endometriose have been identified in cell proliferation, inflammation/immune response, angiogensis and altered gene expression, and steroid hormone reaction (Hou *et al*., 2016).

What DNA methylation does in the pathogenesis of PCOS is that of altered epigenetic program due to this covalent alteration. Changes in DNA methylation in women and animal (induced) with PCOS is linked to phenotypic alteration in disease-affected organ (Cui *et al*., 2018; Kokosar *et al*., 2018; Xu *et al*. 2011). Furthermore, the pathology of various conditions, for example, Type 2 diabetes mellitus, neurodegenerative and cardiovascular diseases, PCOS, recurring miscarriage, endomentriosis and cancer have been related with abnormal DNA methylation (Berson *et al*., 2018; Nebbioso *et al*., 2018; Rosa-Garrido *et al*., 2018; Zhou *et al*., 2018). Hanna *et al*. (2013) posited that during embryonic development, a possible cause of pregnancy loss could be due to abnormal DNA methylation. As a consequence, abnormal methylation of ABR, ALCAM, HLA-E, HLA-G, and ISG15 (which are novel genes) may be essential for embryonic progress and development. ABR, a Rho-family small GTPase regulator, plays important role in mitotic processes of human embryonic stem cells (hESCs) (Ohgushi *et al*., 2017). It could be hypothesized that pathological ABR methylation may induces fetal growth delay by interacting with the mitotic processes of hESCs, resulting in recurrent miscarriage. Also, CREB5 has been reported to be a contributor of recurrent miscarriage (Yu *et al*., 2018). Additionally, studies has indicated high DNA methylation in preeclampsia patients' placental tissue and low DNA methylation in the promoter regions of multiple genes may be a sign and/or consequence of early-onset preeclampsia (Jia *et al.*, 2012; Kulkarni *et al*., 2011; Yuen *et al.*, 2010).

Histone modification: Histone modification is a type of post-translational modification (PTM) that occurs when histone proteins are covalently modified. The mechanisms involved in covalently changing these histone modification marks particularly on histone tails, which includes methylation, acetylation, phosphorylation, and ubiquitylation (Minocherhomji *et al*., 2010). The histone code is the aggregate of these changes and the information they communicate, and it acts to inhibit and/or boost gene expression (Das *et al*., 2017). Modification of chromatin structure or enlisting histone modifiers, PTMs done to histones can influence expression of gene. In females, the

alteration of histone modification affects oogenesis, oocyte aging, endometriosis, create aneuploidy in fertilized oocytes and resulted in embryonic death in the uterus (Chamani and Keefe, 2019, Lestari and Rizki, 2016).

Also, histone modification can affect oocyte age. A study carried out by Manosalva and Gonzalez on mouse germinal vesicle oocytes revealed that aged mice had lower levels of histone (H4K12) acetylation compared to young mice (Manosalva and Gonzalez, 2009). However, MII oocytes showed higher levels of histone (H4K12) acetylation in the aged mice compared to young mice (Suo *et al*., 2010). Thus, the level of H4K12 acetylation can hypothetically be used as a biomarker for determining the quality of oocyte. In another study, Akiyama *et al*. (2006) reported aneuploidy in fertilized mouse oocytes which resulted in embryonic death after meiotic histone deacetylation was inhibited in the uterus.

Furthermore, histone modification was also found in female with endometriosis. An examination conducted by Monteiro and his colleagues, using chromatin immunoprecipitation (ChIP) showed down regulation of low acetylation on the H3/H4 at the promoter regions of genes such as HOXA10, ESR1, CDH1 and p21 in endometriosis (Monteiro *et al*., 2014). As a result, changes in these epigenetic modification patterns may result in female infertility.

Biomarkers of reproductive health and Assisted Reproduction Technologies (ART): Different assisted reproduction technologies are evolving towards the treatment of fertility issues in the female reproductive cycle such as ovulation induction with the use of hormones, artificial insemination, IVF, intracytoplasmic sperm injection (ICSI), intracytoplasmic morphologically selected sperm injection (IMSI), preimplantation genetic testing (PGT) and surrogacy (VARTA, 2020). Owing to the improvement in technological aids, scientists have researched scaffolds-based tissue engineering as a promising candidate in the treatment of infertility challenges. Interestingly, biodegradable shells (scaffold) are suitable for cell delivery systems because, they can imitate the extracellular matrix condition, provide an enabling environment for cell multiplication and differentiation, while their cell culture is useful in developing some organs of the female reproductive system (Jahanbani *et al*., 2020). More so, the in-vitro spermatogenesis by scaffolds is also promising towards improving pregnancy outcomes in clinical settings. The findings of Ding *et al*. (2018) reveals that collagen scaffold based on umbilical cord mesenchymal stem cells (collagen/UC-MSCs) can activate primordial follicles in vitro via phosphorylation of FOXO3a and FOXO1 to achieve a successful pregnancy for women with premature ovarian failure.

More so, the introduction of technologies based on regenerative medicine is another crucial aspect of scientific intervention for treating several types of fertility disorders. This field has gained attention towards the engineering of reproductive tissues in animal models with tremendous results, however, the initiation into the human model is still evolving (Sadri-Ardekani and Atala, 2015). In some other strategies, Gaskins *et al*. (2014) showed that higher intake of folic acid was linked with increased live birth rates after ART treatment. The reports of Nilsson *et al*. (2020) implied that the extended human leukocyte antigen (HLA) class Ib have medical application in reproduction since the untranslated region-4 of HLA is connected to time of pregnancy in female undertaking infertility treatment. Jha *et al*. (2016) found out that multiwalled carbon nanotubes (MWCNT) can efficiently be used for diagnostic reproductive health biomarker development and an effective drug delivery carrier system without disrupting the sperm lipid membrane, thereby opening ways for nanostructured materials for fertility treatments. Meanwhile, Kofod *et al*. (2017) identified that bounty of endometrial uNK cells in the pre-implantation endometrium appears to be imperative for normal fertility and pregnancy success, and may be deployed as medical indicators to envisage implantation success in IVF.

Recently, probiotic therapy is a novel strategy in the reproductive microbiome that can influence conception and pregnancy but currently holds limited evidence on oral probiotic therapy in women with subfertility. The systematic review of Corbett *et al*. (2021)holds that there is contradictory evidence on the efficiency of vaginal probiotics in improving the rates of clinical pregnancy, however, oral probiotic therapy may be helpful to optimize the movement of sperm.

Discussion (old biomarkers vs new biomarkers of female infertility): Several biomarkers of female infertility have been identified over the years. One of the oldest biomarkers identified is the pregnancy-specific β-glycoprotein or Schwanger schaft protein 1 (SP1) (Wahid *et al*., 2017). The 3-D protein profiling coupled with label-free quantitation of ectopic pregnancy systematically studied by Beer *et al*. (2011) detected the serum biomarkers, ADAM12 and ISM2, and five isoforms of pregnancy-specific β-1-glycoprotein family. Meanwhile, the combining of inflammatory cytokines IL-6, IL-8, and TNF-αhas predicted ectopic pregnancy with an 100% and 52.9% specificity and sensitivity respectively. Notwithstanding, the combination of markers with manifold biological functions has demonstrated better outcomes (Rausch and Barnhart, 2012). Tortorella *et al*. (2014) deciphered that a mixed prescription of IL-6 and TNF-α in menstrual discharge is appropriate for screening chronic endometritis in infertile women; and asserting that chronic endometritis is connected with distorted endometrial paracrine milieu,

characterized by majorly T_H1 cytokine profile sustaining an appropriate level of proinflammatory cytokines in the blood from menstrual flow.

More so, Jung *et al*. (2012) identified biomarkers including Vitellogenin (VTG), Complement C3, Ornithine Decarboxylase, pS2, Mucin 1, progesterone receptor and CaBP-9k as a promising biomarker for assessment of the plausible effects of endocrine disruptors. In a small sample study (n=75), Wang *et al*. (2013) showed that placental proteins, PP-14, play a major role in the pathogenesis of endometriosis by reducing serum PP-14 and cancer antigen, CA-125 concentrations after surgery and furthermore after using GnRHa therapy.

However, the lack of sufficient biomarker systems that are of high quality or specific procedures for assessing the effects of biomarkers of effects and small sampling population (pilot study) has necessitated further research in identifying new and effective biomarkers for the determination of biologically and physiologically pertinent concentrations of these toxic compounds. Munnangi *et al*. (2014) appraised pregnancy associated plasma protein-A2 (PAPP-A2) as an added maternal serum marker in prenatal screening for Trisomy 21. The results show that both PAPP-A2 mRNA and protein expression were improved in Down syndrome placentae as compared to diploid placentae. In another study, Shen *et al*. (2015) discovered that serum adipokines levels are not good markers for PCOS. However, a low level of sex hormone-binding globulin should be crucialin the pathogenesis of the medical complications observed in women with PCOS. Eline (2015) added that salivary progesterone and salivary estriol may be considered as useful indicator for imminent delivery in pregnant women and an additional parameter that supports the usefulness of salivary progesterone respectively; meanwhile, estriol can be employed to initiate delivery process and to provide information about the wellbeing of the fetus.

Conclusion and outlook

Infertility concern is a global menace with a serious burden that arises from different environmental factors and disease conditions, however, female infertility is not a death sentence. Therefore, there is a need for increasing awareness of the different existing medical remedies and biomarkers for the condition as outlined in this review. Firstly, accepting the condition without panic is a bold step to the healing process. Then, identifying the cause of the condition for urgent medical care will avert potential future health risks and fatality. Also, there is a need for extensive investigations to unturn the conflicting evidence existing in the association between the different biomarkers (of exposure and effects) and female infertility concerns to overcome the impending reproductive challenges that may arise from prolonged exposure to trace amounts of toxic environmental pollutants like xenobiotics, heavy metals, pesticides, etc. Moreover, numerous animal studies and questionnaire surveys on these biomarkers have been reported with scanty reports on human study, thereby opening the avenues for more research to be conducted to ascertain the level of female infertility via a human experimental approach.

In addition, epigenetics seems to be an evolving field of biological sciences that is opening up innovative research grounds towards the sequential understanding of the human genomic sequence, the interaction between genes and the environment as well their roles in the pathophysiology of various human disorders. Notwithstanding, this aspect is crucial towards identifying disease conditions and proffering treatment available options. Also, the interdisciplinary collaboration between biological scientists and materials scientists towards the fabrication and development of biodegradable scaffolds-based composites and nanomaterials as drug delivery vehicles will assist in supplementing available clinical strategies.

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