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Mini Review

Poly-ADP-Ribose Polymerase (PARP) Inhibitors and Gonad Function: A Mini-Review

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Abstract

Poly(ADP-ribose) polymerase (PARP) plays an important role in DNA repair and other cellular processes. Tumor cells with defects in DNA repair pathways are highly sensitive to the inhibition of PARP activity. So far, four PARP inhibitors (PARPis) have been approved for the treatment of several types of cancer with BRCA mutations; moreover, PARPis have also shown therapeutic potential in treating non-oncological diseases. Therefore, many young patients will be exposed to PARPis and may need to be maintained on these treatments for a long duration, many of whom are of reproductive age. However, the impact of PARPis on ovarian and testicular function remains unclear. In this review, the effects of PARPis on the gonads, fertility, and their mechanisms are discussed, highlighting the significance of further investigation into gonad monitoring indices and protective approaches related to PARPis treatment.

INTRODUCTION

Since Olaparib was first approved in 2014, PARPis has become the standard of care for eligible patients with ovarian, breast, pancreatic, and prostate tumors. To date, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have both approved four PARPis, they are olaparib, niraparib, rucaparib, and talazoparib [1]. PARPis is also currently undergoing clinical trials in combination with radiotherapy, chemotherapy and immunotherapy to treat tumors [2]. These trials may provide new opportunities to expand the utility of PARPis and improve their efficacy in cancer treatment. In addition to malignant tumors, PARP1 activity has been associated with the development of various diseases, including stroke, circulatory shock, myocardial ischemia, nervous system disorders, and liver-related diseases [3,4], suggesting that PARP1 may be a potential target for the treatment of these diseases [3]. Therefore, the therapeutic benefits of PARPis have also been observed in non-tumor diseases, primarily including inflammatory and immune-related diseases that affect vital organs such as the liver, lungs, and heart. Most PARPis share a similar mechanism of action, selectively targeting and killing BRCA-deficient cancer cells by inhibiting PARP1. However, their primary targets and adverse drug reactions can vary [5]. Current studies on the side effects of PARPis mainly focus on the hematologic and cardiovascular systems [5,6]. The main adverse reactions associated with PARPis are primarily in the blood system, including anemia, thrombocytopenia, and neutropenia [5]. In addition, the increased risk of myelodysplastic syndrome and acute myeloid leukemia is a serious adverse effect of long-term use of PARPis [7,8]. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea; discomfort and fatigue [6]; renal insufficiency [9]; And taste disorders [7] are also notable concerns. Furthermore, the potential effects of PARPis on gonadal function and fertility are still poorly understood and have been largely unaddressed in previous studies [10]. Healthcare professionals, including doctors, should advise patients about potential threats to fertility as early in the treatment process as possible to provide the widest range of options for preserving fertility [11]. This article reviews the effects of PARPis on gonadal function and fertility, including their mechanism of action, and discusses the prevention and treatment of the harmful effects of PARPis on male and female gonads.

PARPs and gonads

Maintaining the integrity of germ cell DNA is essential for reproduction and fertility. PARP1-catalyzed PARylation is involved in a variety of biological processes, including DNA damage repair, chromatin organization, chemical resistance, transcription control, mRNA stability, and DNA methylation [1].

The role of PARP in spermatogenesis and sperm maturation in ejaculated sperm [12,13], and is also critical in ovulation and follicular formation [10,14].

Effects of PARP on female reproductive function: PARP affects female reproductive function mainly by influencing follicle formation and ovarian reserve [Figure 1] [10]. PARP1 is essential for oogenesis and follicular formation [15]. A recent clinical study on primary ovarian insufficiency (POI) even found that inhibiting PARP1 expression could reduce the proliferation of ovarian granulosa cells (GCs) [16]. Furthermore, PARP1-mediated endoplasmic reticulum stress (ERS) in GCs helps identify subsets of dormant primordial follicles that can be awakened. Inhibition of PARP1 catalytic activity protects the original follicular pool from excessive ERS in GCs caused by fetal Bisphenol A exposure [14]. The expression of miRNA and mRNA in GCs of women with biochemical POI was detected using microarray technology. Both PARP1 and XRCC6 show lower levels in the GCs of biochemical POI patients, indicating that PARP1 and XRCC6 may be two new targets for the treatment of POI [16]. Additionally, PARP-1 plays a key role in maintaining chromosome stability during the critical phase of meiosis in the female germ line. In metaphase II, oocyte PARP-1 is required to regulate centromere structure and function through mechanisms involving the recruitment of the BUB3 protein into the centromere domain [17].

It is worth noting that radiation triggers ovarian inflammatory processes by enhancing the expression of NF-κB and PARP-1 [18]. Resveratrol is a silencing mediator of the SIRT1 (sirtuin 1) pathway that counteracts inflammatory signals associated with radiation-induced premature ovarian failure (POF). The activation of SIRT1 expression by resveratrol is associated with the inhibition of inflammatory cytokines mediated by PARP-1 and NF-κB. Additionally, resveratrol restores ovarian function by increasing anti-Müllerian hormone (AMH) levels and reducing ovarian inflammation [19,20]. Furthermore, resveratrol can protect the ovaries from cisplatin-induced toxicity by preventing the loss of AMH-secreting granulosa cells and reducing PARP-1 expression, thereby downregulating inflammatory and apoptotic events associated with cisplatin-induced toxicity [21]. Thus, the role of PARPs in ovarian function appears to be contradictory and multifaceted, varying in specific physiology environments.

Effects of PARP on male reproductive function: DNA damage in spermatozoa is an important cause of male infertility; sperm DNA damage is susceptible to sperm DNA damage both during spermatocyte formation and under oxidative stress, so the involvement of PARP in DNA repair in spermatocytes is crucial for male fertility [13,22].

Large amounts of PARP are present in testicular germ cells, the peripheral cell layer of proliferating spermatogenic contains PARP1, and large amounts of PARP2 are present in the seminiferous tubules [22,23]. PARP-2 plays an important role in meiosis I and haploid gamete differentiation, during which PARP-2(-/-) spermatozoa are severely damaged and exhibit significant delayed nuclear elongation [22]. PARP regulates DNA repair and protein levels during spermatocyte formation, and plays an important role in maintaining sperm DNA integrity. DNA damage repair via PARP has been demonstrated in rat germ cells, whereas the use of PARPis results in delayed DNA damage repair [24]. In a human study PARP1, PARP2 were found to be highly expressed in mature spermatozoa and in spermatozoa of men with proven fertility [25]. Cysteine proteases cleave PARP and inactivate its DNA repair function. High levels of cleaved PARP (cPARP) are present in the sperm of infertile men [12]. Excessive oxidative stress causes DNA damage in sperm and increases the risk of genetic diseases thus affecting male fertility [26]. In the presence of excessive DNA damage under conditions of oxidative stress, PARP becomes over-activated and leads to tissue damage and cell death [13,27]. PARP1 and PARP2 regulate the function of topoisomerase Iβ during mouse spermatogenesis, and both genetic and pharmacological PARP inhibition lead to increased TOP2B activity in mouse spermatocytes in vivo [28]. In a study

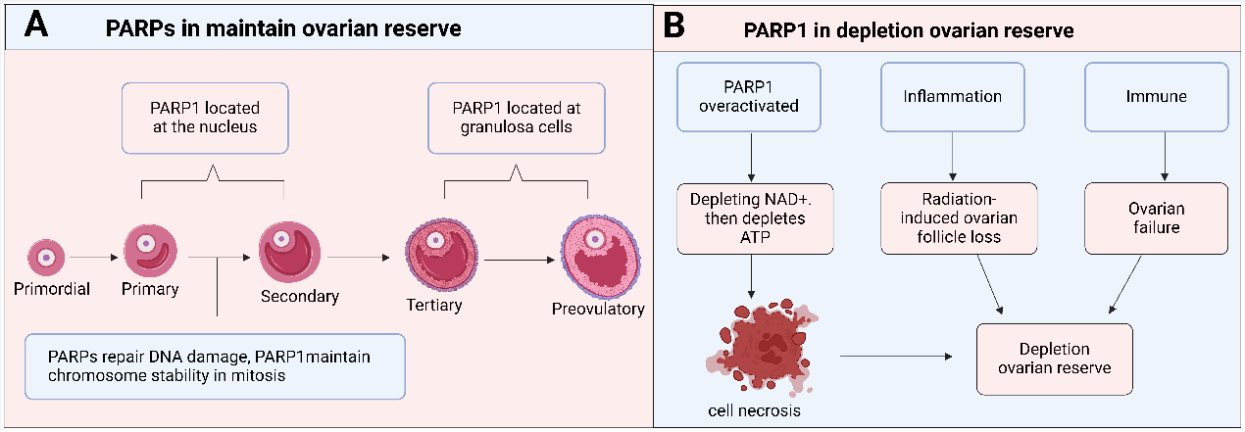

Figure 1 Effects of PARP on female reproductive function. A: PARPs in maintain ovarian reserve. B: PARP1 in depletion ovarian reserve [10].

where DOX injection triggered oxidative stress, it was found that PARP-1 overactivation may lead to testicular damage in mice, and that PARP overactivation leads to a high depletion of sperm ATP, which reduces sperm viability [29]. A study examining the effects of avermectin on rat testes similarly suggested that oxidative stress-mediated PARP activation may be responsible for avermectin-induced testicular damage and affect sperm kinetics [30]. Thus PARPis may protect against testicular damage caused by oxidative stress.

Male infertility is a continuing concern in modern society, and further studies of PARP mechanisms may provide additional solutions to the problems of male reproductive health and infertility.

PARPis Impact on Ovary and testicle

Thanks to advances in treatment, the number of cancer survivors has increased. The 2013 American Society of Clinical Oncology guidelines classified chemotherapy and radiotherapy as treatments that may cause gonadal damage [11,31]. PARPis are promising drugs that may be used for long-term maintenance therapy in more patients in the future. However, their effects on gonads and fertility have been poorly studied [Table 1].

Effects of PARPis on Ovary: PARP1 and its downstream molecule, poly (ADP) -ribose (PAR), have been consistently found within the oocyte nucleus during follicular development [15]. Consequently, the use of PARPis may lead to ovarian damage and a decrease in follicular count. As indicated in Table 1, various studies have explored the impact of PARPis on ovarian health, both in isolation and in combination with radiotherapy, chemotherapy and other anti-tumor therapy [32,33].

In in vitro studies, mouse ovarian tissue cultured with olaparib demonstrated a decrease in the expression levels of GCs markers, alongside a suppression of estradiol production in GCs and alterations in GCs morphology. Olaparib treatment significantly diminished the overall count of follicles, including primordial, primary, early secondary, and late secondary stages, while concurrently increasing the number of atretic follicles. Notably, the reduction in follicles containing GCs was found to be dose-dependent in relation to the amount of olaparib administer [33]. In studies involving mice treated solely with olaparib or in conjunction with a single intraperitoneal chemotherapy agent, it was observed that Olaparib led to a significant reduction of over 35% in primordial follicles. However, it did not impact other categories of follicles, serum AMH levels, luteal counts, or estrus cycles. Mice administered with olaparib exhibited notably enlarged ovaries containing residual primordial follicles, alongside an increase in γH2AX lesions among the surviving oocyte population. Importantly, olaparib did not worsen the follicle depletion induced by chemotherapy [32]. Furthermore, recent findings indicate that PARP1 enzyme inactivation results in heightened genomic instability, as it predominantly obstructs DNA repair in selective pathways distinct from the action of wild-type PARP1, revealing significant physiological differences between PARP1 inactivation and deletion [34]. This discovery also sheds light on a novel mechanism behind the side effects associated with PARPis.

Research has revealed that PARPis exhibit contrasting effects by both preventing and alleviating fibrosis [35], which is indicative of tissue aging. In the aging ovarian stroma, there is an observed increase in inflammatory cytokines and fibrotic tissue [36,37]. Fibrosis serves as an early marker of aging within the ovarian interstitial; notably, older fertile mice display significantly elevated expression levels of several key genes associated with inflammation in their ovaries in comparison to their younger counterparts. Additionally, the presence of multinucleated macrophage giant cells in the ovarian stroma is a hallmark of chronic inflammation exclusively in reproductively

Table 1: The effects of inhibit PARP impact on Ovary and/ or testicle related studies

Study models	Intervention	Major findings	References
Mice ovaries in vitro	Cultured with Ola	↓ Gene of GC markers; ↓ E2 in GC; ↓ markers of GC; ↑ abnormal morphology GC; ↑ follicular atresia	[33]
Mice	Chemotherapy and Ola	↓ Primordial follicles; ↑ Primordial follicle remnants; ↑ γH2AX foci; ↔ serum AMH, corpora lutea number, oestrous cycling	[32]
iMEF cells	Parp1+/A cells	↑ sister chromatid exchange; ↑ mitotic bridges; ↑ hypersensitive to base damages, radiation, and TOP I and II inhibition.	[34]
Rat model of POF	γ-radiation and Res	↓ PARP1; ↑ serum AMH; ↑ primordial follicles; ↓ percentage of atretic follicles; ↓ NF-κB p65; ↓ IL-6 and IL-8; ↑IL-10	[20]
Rat model of POF	Res	inhibit PARP1; ↑ serum AMH; ↓ visfatin RNA level; reserves ovarian follicle pool	[19]
Rat	Cis and Res	↓ PARP1;↓ follicular impairment; ↓ follicular loss; ↑ serum AMH; ↓ inflammatory; ↓ apoptotic	[21]
Mouse	Treatment with 5-AIQ	↑ oocyte numbers; ↑primordial follicle; ↑ mRNA of Bmp15 and Bmpr1b; ↓ mRNA of Grem1 and Per1	[15]
Mice	PARP-2-deficient	impaired spermatogenesis, apoptosis at pachytene and metaphase I stages; defective MSCI; delay in nuclear elongation	[22]
Mice	Treatment with PJ34	Abnormal sperm cell development, apparent failure to perform normal nuclear elongation	[38]
Diabetic rats	Treatment with 3-AB	restored erectile function; ↓PARP activity; ↓corporal apoptosis; ↑ smooth muscle contents; ↑ P-Akt, P-Bad, Bcl-2, ATP and NAD+	[39]
Diabetic rats	Treatment with 3-AB	↓PARP activity; ↑total eNOS , ↑ p-Akt; ↑NO generation; ↑cGMP levels	[40]
Diabetes mice	Treatment with GPI 15427	GPI 15427 corrected a modest diabetic deficit in sensitivity to nitroprusside and acetylcholine-induced relaxation.	[41]
ECS of WL	Addition of 3-AB	Decreased embryo survival	[42]

Ola, Olaparib; E2, estradiol; GC, granulosa cells; TOP, Topoisomerase; AMH, Anti-Mullerian Hormone; POF, premature ovarian failure; Res, resveratrol; Cis, Cisplatin; 5-AIQ, 5-Aminoisoquinolinone; MSCI, meiotic sex chromosome inactivation; 3-AB, 3-aminobenzamide;ECS, Embryos of cryopreserved spermatozoa; WL, weather loach

aged mice [37]. Resveratrol has been shown to mitigate the inflammatory response associated with ionizing radiation-induced POF by suppressing the antagonistic interaction between SIRT1 and PARP-1. This mechanism regulates NF-κB p65, inflammatory mediators, and contributes to restoring serum AMH levels, increasing the pool of primordial follicles, while diminishing the incidence of atretic follicles post-radiation exposure [19,20]. Supporting this, resveratrol also offers protective effects on ovaries against cisplatin-induced toxicity by preserving AMH-secreting GCs, lowering PARP-1 expression, and down-regulating inflammatory and apoptotic processes linked to cisplatin toxicity [21]. Moreover, when administered to mice, 5-aminoisoquinolinone, a PARPis, significantly enhances the quantity of oocytes and original follicles, demonstrating similar benefits in older post-pubertal mice. Further investigations are necessary to elucidate the precise mechanisms at play with 5-aminoisoquinolinone. Simultaneously, there is an increased expression of certain genes and pathways in mouse ovaries, particularly those belonging to the transforming growth factor superfamily [15]. PARPis have demonstrated the ability to prevent and mitigate fibrosis in critical organs such as the lungs, heart, liver, and kidneys [35], However, it is unfortunate that the effectiveness of PARPis in both the prevention and treatment of ovarian fibrosis and inflammation remains inadequately understood.

PARPis exhibit ovarian toxicity, which manifests in both direct effects—without impacting angiogenesis—and indirect effects—by influencing angiogenesis—on ovarian follicles [10]. This toxicity subsequently reduces the survival and production of follicles, ultimately contributing to infertility due to diminished ovarian reserve and dysfunction of granulosa cells [32-34]. Notably, decreasing PARP expression has shown promise in alleviating ovarian damage associated with radiotherapy and chemotherapy [19-21].

Effects of PARPis on testicle: The main function of sperm is to pass the paternal genome to the metaphase II oocyte, ensuring that genetic information is passed on to the next generation. For successful fertilization and healthy offspring, sperm DNA must be protected from exogenous damage. Disruption of poly (ADP-ribose) homeostasis affects spermatogenesis and sperm chromatin integrity in mice [43], so the application of PARPis has potential implications for testicular function and sperm survival [Figure 2][13].

The poly (ADP-ribose) polymerases PARP1 and PARP2 regulate the function of topoisomerase iβ (TOP2B) during mouse spermatogenesis The different tendencies of PARP-1 and PARP-2 to self-modify and/or catalytically ether modify in terms of the number of enzyme molecules involved and the number of bound polyribose (ADP-ribose) may play different roles in the regulation of spermatocyte function [44]. Poly (ADP-ribose) metabolism is essential for proper nucleoprotein exchange during mouse spermatogenesis, and examination of testicular tissue during PJ34 treatment showed abnormal sperm development and a marked failure of normal cell nucleus

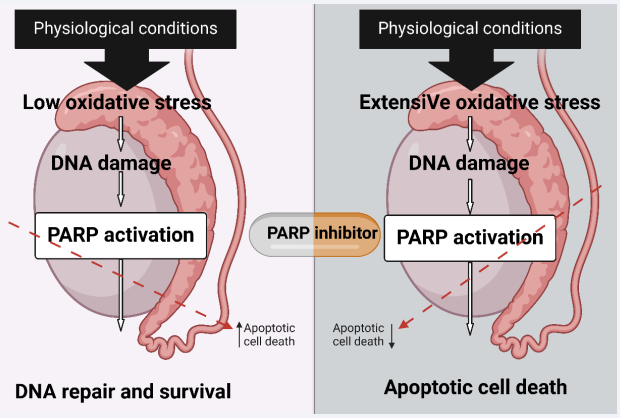

Figure 2 Possible role of PARP activation in testis. Under physiological conditions, mild DNA damage is repaired by PARP activation, PARPis may inhibit DNA repair and lead to apoptic cell death. Pathological conditions, associated with more sever oxidative stress, may cause excessive PARP activation and result in apoptic cell death, PARPis in pathological conditions may prevent apoptic cell death [13].

elongation [38]. The PARP-2-/- mice did show poor fertility, while the PARP-1 knockout mice did not [44]. Male mice deficient in PARP-2 have low fertility due to abnormalities in meiosis I and spermatogenesis, with increased apoptosis in the testes [22]. It is worth noting that sperm DNA damage caused by freezing can be repaired by PAPR, and in a study of frozen preservation of fish embryos, PAPRi was found to reduce the survival rate of embryos even more significantly [42]. We were surprised to find that the erectile function of diabetic rats was impaired and excessive activation of PARP pathway promoted apoptosis in corporal cells through energy consumption, inhibition of Akt phosphorylation and activation of mitochondrial apoptosis pathway. 3-AB (PARPi) inhibition restored erectile function by inhibiting apoptosis of smooth muscle in diabetic rats [39]. Further studies suggested that the over-activation of PARP pathway in the cavernous body of diabetic rats was involved in the erectile dysfunction caused by the cavernous endothelial dysfunction and the abnormal NO/cGMP pathway [40]. Moreover, PARPis can reverse nitrergic neurovascular dysfunctions in penile erectile tissue from streptozotocin-diabetic mice [41].

PARPis is very effective in the treatment of various cancers, but the effect of PAPRi on testicles and sperm should also be paid attention to. In view of the limitations of the current study in Table 1, future research should focus on seeking more effective and less harmful treatment options to ensure the efficacy while mitigating the adverse effects on testicular function.

ARPis effect fertility and embryonic development

Both PARP-1 and PARP-2 are essential for proper embryonic development [45-47]. Additionally, the ADP ribosylation activity of these proteins is linked to crucial physiological processes that contribute to successful pregnancy outcomes [48]. Research on the impact of PARPis on fertility and embryonic development has been conducted (Table 2), providing valuable insights to minimize serious adverse events in clinical applications of PARPis.

Table 2: The effects of inhibit PARP impact on fertility and embryonic related studies

Study models	Intervention	Major findings	References
Porcine IVM	3-ABA cultured COCs	↓ full cumulus expansion; ↓ developmental rate; ↓ total cell number; ↑apoptotic index in parthenogenetically activated embryos	[49]
Mouse	E988A, Parp1+/A	↑ embryonic lethality; ↑ genome instability	[34]
Mice	PARP1+/ΔC	embryonic lethality between embryonic day E8.5 and E13.5	[50]
Mice	Treated with Ola	↓ extracted oocytes; ↓ fertilization rate of IVF; follicle depletion	[33]
Mouse	parp-2(-/-) mutant	↑ embryonic fibroblasts genomic instability by alkylating	[47]
	parp-1(-/-)parp-2(-/-) mutant	die at the onset of gastrulation	
	parp-1(+/-) parp-2(-/-) mutant	female embryo lethality	
Mice	Genetic ablation Parp1 and Parp2 in uterus	compromises maternal decidual response, causes infertility or severe subfertility	[48]
Mice	EB-47(PARPi) intrauterine injection	↓ embryo implantation sites; ↓ blastocysts; ↓ STAT3 of implantation site	[45]
Porcine Embryos	3-ABA cultured vitro fertilized embryos	↓ enlarged blastocysts proportion; ↓ blastocysts total number; ↑ apoptosis index; ↓ autophagy genes; ↓ LC3 protein	[51]
Mice	injected with 5-AIQ	↑ fetuses; the fetuses no distinguishable abnormalities	[15]

IVM, in vitro maturation; COCs, cumulus-oocyte complexes; 3-ABA, 3-aminobenzamide; IVF, in vitro fertilization; STAT3, Signal transducer and activator of transcription 3; LC3, Light Chain 3; 5-AIQ, 5-Aminoisoquinolinone.

In studies involving double mutant mice lacking both parp-1 and parp-2, it was observed that they do not survive past the initiation of gastrulation. Notably, a specific pattern of embryonic lethality was identified in female parp-1(+/-) parp-2(-/-) mutants at embryonic day 9.5 (E9.5). Further investigations revealed distinct X-chromosome instability in these females, a phenomenon not present in their male counterparts [47]. PARylation is crucial for regulating oocumulus expansion via gene expression modulation, which in turn influences both the developmental capability and quality of parthenogenetic embryos. In COCs treated with 3-ABA, full cumulus expansion was achieved; however, there was a marked reduction in developmental rate and total cell count, along with an increased total apoptotic index in parthenogenetically activated embryos [49]. The inactivation of PARP1 has been linked to embryonic lethality and genomic instability in mice, acting in a dominant negative fashion [34]. This aligns with findings that mutations resulting in the inactivation of PARP1 led to embryonic death occurring between embryonic days 8.5 and 13.5. Interestingly, while the introduction of the PARP1-ΔC mutation in adult mice did not adversely affect their survival, it did render them susceptible to reactions from alkylating agents [50]. In a comparison of IVF outcomes for olaparib mice, the olaparib group exhibited a significantly reduced number of oocytes and fertilization rates in comparison to the control group. However, upon cessation of the drug, a recovery in the number of oocytes was observed in the olaparib group [33]. This aligns with findings that PARylation plays a crucial role in the selective autophagic degradation of ubiquitinated proteins, thereby aiding the survival of in vitro derived porcine embryos, while 3-aminobenzoamide (PARPi) was shown to inhibit blastocyst development [51]. Furthermore, PARP is implicated in modulating uterine receptivity and facilitating the decidualization of stromal cells [45,48]. During the implantation phase, the natural form of PARP1 in both the cytoplasm and nuclear compartment at implantation and non-implantation sites was found to be upregulated on day 5, coinciding with increased transcription levels of PARP1. Notably, the use of EB-47(PARPi) to inhibit PARP1 activity resulted in a reduction of implantation sites and blastocyst counts on day 5 [45]. Genetic deletion of Parp1 and Parp2 in the uterus negatively impacts the maternal decidual response, leading to infertility or severe subfertility, although it does not affect embryo localization or attachment [48]. Contrarily, other studies indicate that females treated with 5-Aminoisoquinolinone (PARPi) delivered a significantly higher mean number of fetuses ($P < 0.05$), with no evident abnormalities observed in the fetuses [15].

PARP-1 and PARP-2 are critical in regulating physiological processes that contribute to successful pregnancy [45-47]. The inhibition of PARP activity can hinder autophagy and other mechanisms essential for embryonic development, consequently leading to reduced embryonic growth [33,51]. Additionally, this inhibition can result in pregnancy loss by affecting the process of decidualization [48], despite a limited number of studies indicating contrary findings [15]. It is imperative to conduct further research on the impact of PARPis on fertility and embryonic development to mitigate adverse pregnancy outcomes.

Prevention and Protection of gonads Function

It is imperative that medical professionals engage in early discussions regarding the potential for infertility with cancer patients in their reproductive years, as well as with the parents or guardians of affected children [11]. For men who have reached puberty, sperm cryopreservation is a viable option that should be implemented prior to the commencement of chemotherapy. Adult women have access to several methods aimed at preserving ovarian function, including embryo cryopreservation, unfertilized oocyte cryopreservation, ovarian transposition, conservative gynecologic surgeries, ovarian suppression using GnRHa, and ovarian tissue cryopreservation and transplantation [11,52]. In the case of prepubescent children, cryopreservation of ovarian and testicular tissues remains the sole option for fertility preservation, although these methods are still under investigation [11].

Regarding PARPis, further investigation is required to identify effective prevention and treatment strategies for any negative impacts on gonad function. Initially, the selection of combination therapies is crucial; evidence suggests that PARPis can mitigate ovarian damage induced by radiotherapy and cisplatin [19-21]. However, it is important to note that alkylating agents like cyclophosphamide and hydrophobic drugs pose greater toxicity to the ovaries compared to other medications [31], so the simultaneous use of PARPis with alkylating agents should be minimized. Secondly, managing the dosage and duration of PARPis treatment is essential. The chemotherapy dose and treatment duration are significant dose-dependent factors influencing gonad health. Patients with BRCA mutations or homologous recombination deficiency are particularly sensitive to PARPis [53], leading to the hypothesis that PARPis may induce more significant follicle depletion in these individuals. Recent studies indicate that Niraparib offers comparable progression-free survival benefits when dosing is tailored to individual body weight and platelet counts [54]. Consequently, additional research and clinical trials are necessary to explore the potential for dosage adjustments in these patients while still effectively addressing tumor growth. Furthermore, a patient's age plays a critical role, as older women typically possess a reduced primordial follicle reserve and are at a higher risk of ovarian failure during or after treatment [55]. Therefore, women with fertility concerns, particularly those carrying BRCA mutations, should prioritize fertility preservation as early as possible [56]. Further understanding about the PARP related apoptosis and DNA repair pathways of gonads and embryos is needed for exploring novel approaches for gonads protection.

LIMITATION AND FUTURE PERSPECTIVE

Research focusing on the impact of various PARPis on gonadal health, fertility, and embryonic development remains limited. The incidence of gonadal insufficiency and infertility is a significant adverse consequence of chemotherapy for both adult and pediatric cancer patients [11]. Despite the abundance of clinical trials centered around PARPis, it is regrettable that no studies have specifically addressed ovarian or testicular function as primary endpoints. Furthermore, only a handful of these trials have gathered data regarding ovarian function post-intervention [6,8,57]. It is essential that future research routinely incorporates endpoints related to gonadal function testing for both ovarian and testicular health.

Gonadal dysfunction represents a critical long-term side effect of pharmacological treatments. Recent years have seen advancements in our understanding of the sterility risks faced by both adults and children undergoing chemotherapy. Given that PARPis are anticipated to become more accessible to younger patients, the implications of these drugs on gonadal function and embryonic development are especially noteworthy. The dual nature of their effects must be recognized [10]. Clinically assessing ovarian and testicular damage through established reserve markers can enhance the awareness of oncologists and patients regarding the potential infertility risks associated with this therapy, thus facilitating informed discussions about fertility preservation strategies. Fertility counseling must be customized to meet the individual needs of patients, taking into account factors such as age, BRCA mutation status, ovarian and testicular reserve, as well as the type and dosage of the chemotherapy regimen [52]. Furthermore, it is essential to explore strategies for safeguarding the ovaries and testicles from potential harm. Lastly, the impact of PARPis on fertility outcomes, including pregnancy rates and live birth rates, warrants thorough investigation.

CONCLUSION

PARPis are antitumor drugs used in BRCA mutation cancer patients, notably younger patients, who have a desire for future fertility. PARPis may inhibit primordial follicle survival, resulting follicular loss or granulosa cell dysfunction. On the contrary, PARPis protect ovarian function through anti-immune and anti-inflammation effects. PARPis did not deteriorate ovarian function when combined with other chemotherapy or radiotherapy regimens [32], instead reversing the damage from radiotherapy [19]. Sperm DNA damage is susceptible to sperm DNA damage both during spermatocyte formation and under oxidative stress, so the involvement of PARP in DNA repair in spermatocytes is crucial for male fertility [43,44]; Contrary to this PARPis may protect against testicular damage caused by oxidative stress [13,39]. PARPis can hinder autophagy and other mechanisms essential for embryonic development, consequently leading to reduced embryonic growth [33,51]. Additionally, this inhibition can result in pregnancy loss by affecting the process of decidualization [48], despite a limited number of studies indicating contrary findings [15]. It is imperative to conduct further research on the impact of PARPis on fertility and embryonic development to mitigate adverse pregnancy outcomes. Although there are a great number of clinical trials, few trials have considered ovarian function as a clinical outcome of PARPis treatment [57]. Therefore, exploring the long term effects of PARPis on gonads function and embryonic development, and correspondent protective measures is urgent and substantial.

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