Genomic Consideration in Chemotherapy-Induced Ovarian Damage and Fertility Preservation

Seongmin Kim 1, Sanghoon Lee 2,*, Hyun-Tae Park 2, Jae-Yun Song 2 and Tak Kim 2

1 Gynecologic Cancer Center, CHA Ilsan Medical Center, CHA University College of Medicine, 1205 Jungang-ro, Ilsandong-gu, Goyang-si 10414, Korea; naiad515@gmail.com
2 Department of Obstetrics and Gynecology, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul 02841, Korea; cyberpelvis@korea.ac.kr (H.-T.P.); yun1105@korea.ac.kr (J.-Y.S.); tkim@kumc.or.kr (T.K.)
* Correspondence: mdleesh@gmail.com; Tel.: +82-2-920-6773

Abstract: Chemotherapy-induced ovarian damage and fertility preservation in young patients with cancer are emerging disciplines. The mechanism of treatment-related gonadal damage provides important information for targeting prevention methods. The genomic aspects of ovarian damage after chemotherapy are not fully understood. Several studies have demonstrated that gene alterations related to follicular apoptosis or accelerated follicle activation are related to ovarian insufficiency and susceptibility to ovarian damage following chemotherapy. This may accelerate follicular apoptosis and follicle reservoir utilization and damage the ovarian stroma via multiple molecular reactions after chemotherapy. This review highlights the importance of genomic considerations in chemotherapy-induced ovarian damage and multidisciplinary oncofertility strategies for providing high-quality care to young female cancer patients.

Keywords: chemotherapy; gene; mutation; gonadotoxicity; fertility preservation; cryopreservation; oncofertility

1. Introduction

It is estimated that 9.2 million women were newly diagnosed with malignancy worldwide in 2020 [1]. Among adolescents and young adults aged 15–39 years, 89,500 patients were newly diagnosed with cancer, and 9270 mortalities were reported in the United States [2]. In these patients, oncologic therapies can harm normal ovarian function and result in ovarian damage [3]. Fertility preservation is now an emerging discipline that plays a critical role in preventing infertility in the care of young cancer patients [4,5].

Chemotherapy could harm gonadal function in young cancer patients and cause loss of the ovarian reserve [6]. The molecular mechanism of chemotherapy-induced ovarian damage has been investigated to understand and prevent gonadotoxicity in cancer treatment [7]. However, the genetic aspects of chemotherapy-induced ovarian damage are still not fully understood. This article reviews the genetics of chemotherapy-induced ovarian dysfunction and explores the gene-targeted prevention of ovarian damage.

2. Genes Involved in the Regulation of Ovarian Follicular reserve

In females, number of primordial follicles (PFs) declines towards menopause because of their finite nature [8]. In every mammalian species, the ovarian reserve is formed early in life and then declines regularly throughout life [9]. It is created during ovarian histogenesis by follicular endowment [10]. Non-growing follicle endowment is composed of the formation, commitment, migration, and colonization of ovarian primordial germ cells (PGCs). The development of the bipotential gonad is followed by sex determination, definitive ovarian histogenesis, and follicular assembly [11,12]. Figure 1 shows the morphogenesis of follicles from the arrival of primordial germ cells to secondary follicles. The processes and related genes are listed in Table 1 [13–15].
2.1. Primordial Germ Cells Formation and Gonad Colonization

Several studies in mice have investigated important signals for primordial germ cell specification, migration, and proliferation. The deletion of Bmp2, Bmp4, Bmp8a, and downstream mediators such as Smad genes is related to the failure of migration or absence of PGCs [16–20]. Oct4 expresses critical survival factors and forms pluripotent stem cells [21]. Nanos genes also have a specific role in the migration and proliferation of PGCs. Nanos1 ablation was related to the failure of PGC migration, and Nanos3 ablation caused PGC migration and proliferation defects [22,23]. Kitl, Pin1, and Pog are also known to play critical roles in the survival and establishment of PGCs [24–26].

2.2. Germ Cell Survival and DNA Damage Repair

Autophagy has a vital role in the regulation of follicle development. Atg7 and Becn1, which are autophagic factors, are involved in follicular formation [27]. Gja1 encodes connexin 43, which forms gap junctions between cells in the ovigerous cords, and plays a role in PGC development [28]. Genes such as Spo11, Msh4, and Msh5, which are involved in repairing DNA double-strand breaks (DSBs), may affect fertility and induce ovarian insufficiency [29–31]. The DNA strand-related gene Dmc1 is responsible for maintaining follicular count [32]. Another DNA DSB-related gene is Atm, which is related to the loss of follicles and ovarian dysgenesis [33]. The role of Brca1/2, which is critical in homologous recombination to repair DSBs, in ovarian dysfunction is still under debate. Although several clinical studies have shown poor ovarian reserve in Brca1/2 carriers, the exact role of Brca1/2 in the ovarian reserve has not yet been determined [34,35].

Additionally, a loss of follicles is observed after Rec8 ablation, which is a component of the cohesion complex [36]. Loss of Cdk2, which is involved in cell cycle progression, or Ceph, which regulates the synaptonemal complex, is related to germ cell loss [37,38]. Fanc family genes encode proteins that interact to mediate DNA damage repair [39]. Mutations in Fanc family genes may induce Fanconi anemia, thus also contribute to impairment of follicular development [40–42]. Hsf1 induces the expression of heat shock proteins and initiates...
oocyte development. Hsf1 is also responsible for the anti-oxidative stress in oocytes [43,44]. Syce1 is essential for the formation of synaptonemal complexes [45]. Other meiotic gene mutations, including Stag3, Pof1b, Pof2b, and Hfm1, have also been associated with ovarian reserve impairment in humans [46–48].

2.3. Follicular Assembly and Turnover

Non-growing follicular assembly occurs with the degeneration of other oocytes surrounded by squamous pre-granulosa cells and the basement membrane. Mutations in several genes involved in this process could alter the ovarian reserve [15]. Figla, an oocyte-specific transcription factor, is necessary to form primordial follicles. Ablation of this gene results in failure of follicle formation [49]. When this gene is altered, ovarian insufficiency can occur [50]. Neurotrophins are a family of growth factors that regulate cell survival and follicular development. For example, Ngf, Ntrk1, and Ntrk2 affect primordial follicle formation in mice [51]. Additionally, Nt4 and Bdnf are related to follicular assembly and survival [52]. Nf3 and Ntrk3 also participate in the transition of follicles from the PF to the primary stage [53].

Apoptotic pathway-related genes are also related to follicle turnover. Alterations in Casp2 and Bcl2 have been shown to decrease the number of PFs [54,55]. Ahr and Bax play important roles in follicle maturation and PF endowment. Bax deletion is associated with the formation of a better ovarian reserve [56]. However, contradictory results have been reported in the literature [57]. Deletion of Ahr, which is a regulator of Bax expression, results in an increased PF count [58]. Mcl1 is another gene involved in apoptosis. Mcl1 deletion elevated superoxide levels and activated the autophagic pathway, reducing the ovarian reserve [59].

3. Mechanism of Chemotherapy-Induced Ovarian Damage

Chemotherapy-induced ovarian damage may be transient, and menstruation may recover after treatment completion. Oocytes and granulosa cells are vulnerable to chemotherapeutic agents. The possible gonadotoxic chemotherapeutic agents used are shown in Table 2 [7]. Each agent has a different mechanism of action on malignant cells, resulting in the cessation of the cell cycle. With conventional chemotherapy agents, ovarian insufficiency involves PF pool depletion by apoptosis or hyperactivation mechanisms, mediated by the ABL/TAp63 and PI3K/Akt/mTOR pathways [7].

Table 2. Ovarian damage with chemotherapeutic agents and their mechanisms of action.

| Type of Chemotherapy | Agents                  | Target Disease                                                                 | Mechanisms of Action                                                                                      |
|----------------------|-------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Alkylation agents    | Cyclophosphamide        | Leukemia, breast cancer, lung cancer, ovarian cancer, lymphoma, Hodgkin’s disease | Interference with cell division via cross-linking of DNA; Mitochondrial transmembrane potential reduction; Inhibition of the accumulation of cytochrome c in the cytosol; Induction of DSBs in oocytes |
|                      | Ifosfamide              |                                                                                   |                                                                                                          |
|                      | Nitrosoureas            |                                                                                   |                                                                                                          |
|                      | Chlorambucil            |                                                                                   |                                                                                                          |
|                      | Melphalan               |                                                                                   |                                                                                                          |
|                      | Busulphan               |                                                                                   |                                                                                                          |
|                      | Mechlorethamine         |                                                                                   |                                                                                                          |
| Vinka alkaloids      | Vinblastine             | Testicular cancer, lymphoma, Hodgkin’s disease, breast cancer, germ cell tumors, lung cancer | Inhibition of tubulin forming into microtubules; Low gonadotoxic risk                                    |
|                      | Vincristine             |                                                                                   |                                                                                                          |
| Alkylation agents    | Cyclophosphamide        | Leukemia, breast cancer, lung cancer, ovarian cancer, lymphoma, Hodgkin’s disease | Interference with cell division via cross-linking of DNA; Mitochondrial transmembrane potential reduction; Inhibition of the accumulation of cytochrome c in the cytosol; Induction of DSBs in oocytes |
|                      | Ifosfamide              |                                                                                   |                                                                                                          |
|                      | Nitrosoureas            |                                                                                   |                                                                                                          |
|                      | Chlorambucil            |                                                                                   |                                                                                                          |
|                      | Melphalan               |                                                                                   |                                                                                                          |
|                      | Busulphan               |                                                                                   |                                                                                                          |
|                      | Mechlorethamine         |                                                                                   |                                                                                                          |
Table 2. Cont.

| Type of Chemotherapy | Agents                | Target Disease                                      | Mechanisms of Action                                                                 |
|----------------------|-----------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------|
| Vinka alkaloids      | Vinblastine, Vincristine | Testicular cancer, lymphoma, Hodgkin’s disease, breast cancer, germ cell tumors, lung cancer, | Inhibition of tubulin forming into microtubules; Low gonadotoxic risk                  |
|                      |                       |                                                     |                                                                                        |
| Antimetabolites      | Cytarabine, Methotrexate, 5-fluorouracil | Leukemia, breast cancer, ovarian cancer, gastrointestinal cancer | Inhibition of purine, pyrimidine becoming incorporated into DNA; Inhibition of RNA synthesis; Low gonadotoxic risk |
|                      |                       |                                                     |                                                                                        |
| Platinum agents      | Cisplatin, Carboplatin, Oxaliplatin | Bladder cancer, colorectal cancer, head and neck cancer, lung cancer, ovarian cancer, testicular cancer | DNA damage by the formation of DNA adducts, which interfere with cellular transcription and replication, leading to oocyte death. |
|                      |                       |                                                     |                                                                                        |
| Anthracycline antibiotics | Daunorubicin, Bleomycin, Doxorubicin | Lymphoma, leukemia, breast cancer, sarcoma | Intercalation with DNA and prevention of its replication and transcription via the inhibition of topoisomerase II; Upregulation of P53 protein which induces apoptosis; DNA DSBs leading to activation of ATM, which initiates apoptosis |
| Others               | Procarbazine          | Hodgkin’s disease, brain tumor                      | Inhibition of DNA methylation and RNA and protein synthesis                           |

DSB, double-strand breaks.

3.1. Chemotherapy-Induced DNA DSBs

Chemotherapy can result in DSBs in DNA that can be repaired by the ataxia-telangiectasia mutated-mediated DNA damage repair pathway. However, failure of the repair pathway results in cellular apoptosis in growing follicles and proliferating granulosa cells [60]. P63 protein, a transcriptional factor implicated in cancer and development, is also involved in female reproduction [61]. TAp63, which is the N-terminal transactivation domain containing isoform of P63, is responsible for the protection of the female germ line during meiotic arrest [62]. The P63 protein activates BAX and BAK proteins, which can be transmitted by activating Tap73, a P53-upregulated modulator of apoptosis [63]. This damage has been reported to occur even with low-risk gonadotoxic agents [64].

3.2. Burnout Effect

The PI3K/Akt/mTOR pathway directly influences the oocytes and pre-granulosa cells of PFs and indirectly destroys large follicles, called the “burnout effect” [65]. This phenomenon impairs anti-Mullerian hormone (AMH) and reduces the suppression of the PF pool through destroying follicles, which is followed by the activation of PFs to compensate for the decrease in the number of growing follicles [66]. This effect triggers the growth of dormant follicles. It is affected by the upregulation of the PI3K/Akt/mTOR pathway and substantial follicular apoptosis, which reduces AMH secretion [67].

3.3. Stromal and Microvascular Damage

The ovarian stroma can be indirectly damaged by chemotherapeutic agents [8,68]. A previous study reported chemotherapy-induced ovarian stromal fibrosis and vascular damage [69]. Damage to blood vessels and focal fibrosis of the ovarian cortex could be another mechanism of chemotherapy-induced ovarian dysfunction [70]. In patients undergoing chemotherapy, the ovaries show thickening and hyalinization of the cortical vessels [71]. This is also supported by another study that showed an inverse correlation between ovarian vascular density and follicular apoptosis [72], thus suggesting an indirect mechanism by which chemotherapy-induced ovarian vascular injury reduces the number of PFs.
3.4. Genes Related to Chemotherapy-Induced Ovarian Damage

3.4.1. DNA Damage Repair

Homologous or non-homologous DNA repair is involved in the recovery of chemotherapy-induced DNA damage in PFs. Consequently, mutations in genes that regulate these repair pathways could increase the susceptibility to ovarian toxicity due to chemotherapy.

*Brca1* and *Brca2* are critical in the repair of DNA DSBs. *Brca* mutation carriers have not only increased the risk of cancer but also fertility-related issues [73]. *Brca1* mutation carriers show lower AMH levels, but the results are contradictory between studies [74,75]. *Brca2* mutations are not associated with a low ovarian reserve in these studies. On the other hand, a retrospective study on the in vitro fertilization of *Brca* mutation carriers showed no significant differences in the procedure cycles or in the number of oocytes compared to non-carriers [76]. Additional research is warranted to define exact role of Brca mutation in fertility preservation in patients with related malignancy. In cancer patients with *Brca* mutations, poly (ADP-ribose) polymerase (PARP) inhibitors is widely used for the treatment of cancer [77]. The use of PARP inhibitors could negatively affect embryo development [78]. In another study, the gene expression of granulose cell markers was decreased in patients with PARP inhibitor use [79].

Alterations of other genes involved in DNA repair, *Mcm8* and *Mcm9*, can induce primary ovarian insufficiency [80]. *Stag3*, a meiosis-specific gene, is also important in DNA damage repair. A recent study demonstrated that variants of *Stag3* are associated with primary ovarian insufficiency [81]. Similarly, *Hfm1*, *Nup107*, and *Syce1* are associated with DNA repair and are implicated in ovarian insufficiency [45,82,83].

3.4.2. Apoptosis

Dysregulation of apoptosis results in decreased ovarian reserve and an increased possibility of gonadal damage after chemotherapy. *Nanos3*, which expresses an RNA-binding protein that regulates apoptosis to maintain a proper PF pool, was related to ovarian insufficiency in a study of Chinese women with variant mutations [84]. In that study, the level of NANO3 protein was correlated with the number of PGCs. Ablation of another important anti-apoptotic gene, *Bcl2*, is related to a decreased number of PGCs in mice [55]. *Pgrmc1*, which is another candidate gene, has a progesterone-dependent anti-apoptotic action, which is another candidate gene. Mutations in this gene were related to ovarian insufficiency in a previous study [85,86].

3.4.3. Follicular Activation and Development

The possibility of ovarian damage after chemotherapy could also be increased because of genetic mutations involved in follicular activation and development. *Fxo3a* inhibits follicular activation in the ovary. Ablation of this gene in mice is related to early ovarian dysfunction [87]. In humans, *Fxo3a* and *Fxo1a* were identified in women with primary ovarian insufficiency in two studies [88,89]. Variants of another follicle developing gene, *Bmp15*, are associated with ovarian dysfunction, as identified in multiple studies [90–92].

4. Prevention Strategy for Ovarian Damage

Fertility preservation options can be personalized in terms of patient age, desire for conception, treatment regimen, and socioeconomic status [93]. Such options include hormonal medications for ovarian suppression, cryopreservation, in vitro oocyte maturation, artificial ovaries, and stem cell technologies. Additionally, the potential ovarian protective effects of several genetic variants could be considered. Several established options including embryo cryopreservation and oocyte cryopreservation are already in clinical use. However, there are also experimental options including ovarian tissue cryopreservation, oocyte in vitro maturation, artificial ovary, and stem cell technologies [93].
4.1. Consideration for Protective Genetic Variants for Chemotherapy-Induced Ovarian Damage

Several reports have been published regarding the protective effect of gene mutations associated with a better prognosis in terms of ovarian insufficiency. A protective effect of reduced allele frequency of the *Inha* gene promoter was observed in patients with premature ovarian insufficiency [90,91]. In a study involving ovarian insufficiency, increased expression levels of *Mvh*, *Oct4*, *Sod2*, *Gpx*, and *Cat* were detected after resveratrol treatment [94], implying that genes related to ovarian stem cell proliferation or anti-oxidative processes may help protect the ovary against chemotherapy-induced damage. An association between microRNA polymorphisms and the risk of premature ovarian insufficiency was also reported previously. Further investigations are warranted to identify significant protective genes against chemotherapy-induced ovarian damage.

4.2. Genetic Screening of Candidate Markers

Traditional biochemical markers for ovarian reserve include AMH level, follicle-stimulating hormone concentrations, inhibin-B level, and antral follicle count on ultrasound [7]. However, due to the development of genetic testing, several candidate genes for ovarian insufficiency are being investigated [85]. *Fmr1* and *Brca* testing can be performed easily in genetic clinics. Patients with mutations in these genes are at a higher genetic risk at baseline [95]. Evaluation of other frequent genetic variants, including *Nobox*, *Figla*, *Bnc1*, *Sohlh1*, *Sohlh2*, *Foxo3*, and *Hfm1*, could help identify individuals with increased genetic risk of ovarian damage due to chemotherapy. Next-generation sequencing could be considered in ovarian reserve testing by using targeted gene panels, whole-exome sequencing, or whole-genome sequencing [96]. The application of this technique is the future of genetic evaluation of patients who are at high risk of ovarian dysfunction after chemotherapy.

4.3. Other Options for Prevention of Ovarian Damage

4.3.1. Gonadotropin-Releasing Hormone (GnRH)

Ovarian suppression using GnRH agonists before or during chemotherapy has protective effects on the ovaries by regulating the secretion of FSH and luteinizing hormone [97]. Ovarian suppression with this method protects ovarian function in young patients treated for lymphoma, breast cancer, and other diseases [98–100]. GnRH analogs have two possible theoretical mechanisms [101–103]. First, it involves decreasing the sensitivity of PFs entering the growing pool to gonadotoxicity. Furthermore, it constitutes the direct anti-apoptotic effect of GnRH agonists on ovarian germline stem cells. In combination with other modalities, the use of GnRH agonists, including oocyte or embryo freezing, may be a good option [104].

4.3.2. AMH

In a previous study, the initiation of PF growth was inhibited when human ovarian cortical tissue was cultured with recombinant AMH [105]. Combining recombinant AMH with the cyclophosphamide metabolite in an ex vivo culture system maintained a high number of PFs in the ovaries [65]. AMH usually has limited activity in the ovaries, because it is an endogenous hormone.

4.3.3. AS101

AS101 is a non-toxic immune modulator that acts on the PI3K/Akt/mTOR pathway [106]. AS101 was shown to diminish apoptosis in granulosa cells in an in vivo study [107]. AS101 was also related to a reduced follicle activation, thereby increasing follicle reserve and rescuing fertility after cyclophosphamide treatment [107].

4.3.4. Imatinib

Imatinib is a tyrosine kinase inhibitor that selectively inhibits the ABL kinase domain of the bcr-abl oncogenic protein [108]. As PF depletion is mainly mediated by the ABL/TAp63 and PI3K/Akt/mTOR pathways, imatinib might prevent ovarian dysfunction
caused by these pathways [109]. Many studies have investigated the protective effects of imatinib, but conflicting results have been reported [110–112].

4.3.5. Sphingosine-1-Phosphate

Sphingosine-1-phosphate (S1P) inhibits the ceramide-promoted apoptotic pathway by increasing vascularity and angiogenesis and reducing PF apoptosis [72,113]. Co-administration of S1P with cyclophosphamide and doxorubicin was associated with a lower rate of apoptosis in mice [114]. It also showed a protective effect in mice treated with dacarbazine [115]. However, contradictory results were also reported in another study [116].

4.4. Cryopreservation

4.4.1. Embryo Cryopreservation

Embryo cryopreservation is the most well-established method for preserving fertility [117]. Embryo freezing should be considered in patients who desire fertility preservation if there is adequate time for ovarian stimulation and if a partner or donor sperm is available [118]. Previous studies have demonstrated that embryo vitrification methods are better than slow freezing in pregnancy and live birth rates [119–121]. This option is not adequate for prepubertal girls because it requires ovarian stimulation. In studies comparing the fertilization and live birth rates of in vitro fertilization and embryo cryopreservation in patients with cancer, contradictory results were observed [122–125].

4.4.2. Oocyte Cryopreservation

Oocyte cryopreservation is also considered a standard technique for fertility preservation in adolescents and young adults with cancer [126]. The development of freezing techniques in assisted reproductive techniques has improved oocyte cryopreservation outcomes similar to those obtained with fresh oocytes [127,128]. It can also be utilized for women who are unmarried or do not want sperm donation. Vitrification was more effective than slow freezing in reducing cellular damage and chilling injury during the freezing process [129,130]. The combination of oocyte cryopreservation and ovarian tissue cryopreservation can enhance fertility [131].

4.4.3. Ovarian Tissue Cryopreservation and Transplantation

Ovarian tissue cryopreservation could be considered for fertility preservation in children or young patients with cancer who need immediate treatment and do not have enough time for ovarian stimulation. Using this technique, a large number of oocytes can be preserved, and the hormonal functions of the ovary can be protected [132]. Slow freezing has been established as the preferred method for ovarian tissue cryopreservation rather than vitrification [133]. Ovarian activity was restored in 92.9% of the cases after transplantation of cryopreserved ovarian tissue by using the slow-freezing method [134]. Owing to the possible contamination of the ovarian tissue with malignant cells, this procedure is not utilized for patients with ovarian or hematologic malignancies [135,136].

5. Future Perspectives

The mechanism of chemotherapy-induced ovarian damage is not completely understood. Several studies have demonstrated that genes related to apoptosis or accelerated follicle activation are related to ovarian insufficiency. However, contradictory results have been reported. Validation of genetic profile screening for estimating susceptibility to chemotherapy-related ovarian damage may be further warranted. Patients with genetic variants involved in DNA repair or follicle activation can be screened before the initiation of cancer treatment via genetic testing. The establishment of genetic screening for fertility preservation could be helpful for young patients with cancer. Various other options are still under investigation.
Whole-ovarian transplantation has the benefit of immediate revascularization following blood vessel anastomosis [137,138]. Successful whole-ovarian cryopreservation and transplantation have been reported in animal studies [139–142]. However, potential injury due to hypothermic damage to blood vessels and difficulties in dispersing enough cryoprotective agents make it challenging in clinical practice.

In vitro maturation (IVM) can be used in patients with cancer who lack adequate time for ovarian stimulation or prepubertal girls who need immediate treatment. This requires immature oocyte retrieval and cryopreservation at an immature stage or a post-IVM mature state [143]. Several attempts have been reported; however, only a few live births have been reported after IVM procedures in patients with cancer [144–146].

Artificial ovaries can be useful for developing mature oocytes via in vitro culture of oocytes, isolated follicles, and ovarian tissue [147,148]. In animal models, this approach restored endocrine function, enabling in vivo follicle development and successful pregnancy; however, there have been no successful reports in humans [148,149]. Ovarian stem cells are under investigation for use in fertility preservation. Previous studies have reported successful detection and isolation of ovarian stem cells in animals and humans [150,151]. However, it is not commonly applied in clinical practice because of insufficient evidence in humans and ethical issues related to the use of oocytes and embryos [152]. Further studies are required to implement these approaches in clinical practice.

6. Conclusions

Fertility preservation in cancer patients is becoming more important; however, the effects on ovarian damage differ according to the type of agent and from patient to patient. Molecular mechanisms involved in cancer therapy-induced ovarian damage have been studied by many researchers. Understanding the molecular etiology of treatment-induced ovarian dysfunction can aid in identifying targets to prevent and reduce gonadal damage during cancer treatment and increase the number of options for fertility preservation.

The adoption of state-of-the-art genetic testing, including next-generation sequencing, has led to surprising developments in understanding the genomic aspects of ovarian insufficiency. The concept of precision medicine could be utilized to treat cancer and screen patients who have gonads vulnerable to chemotherapeutic agents, making it possible to plan individual fertility preservation options. As the genomic alterations of chemotherapy-induced ovarian damage continue to be investigated, mutations altering related molecular pathways may provide reliable information about reproductive potential.

Additionally, several novel therapies could be utilized in combination with standard FP techniques, or they may be used alone in the future. These strategies can assist young women who are not eligible for conventional methods because of their age or limited time before the initiation of disease treatment.

**Author Contributions:** Writing—original draft preparation, S.K.; writing—review and editing, S.L.; conceptualization and visualization, S.K. and S.L.; supervision, intellectual content, and paper coordination, H.-T.P., J.-Y.S. and T.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the National Research Foundation of Korea Grant by the Korean Government (grant number NRF-2016R1C1B3015250).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* 2021, 71, 209–249. [CrossRef] [PubMed]
Genes 2021, 12, 1525

2. Miller, K.D.; Fidler-Benaoudia, M.; Keegan, T.H.; Hipp, H.S.; Jemal, A.; Siegel, R.L. Cancer statistics for adolescents and young adults, 2020. CA Cancer J. Clin. 2020, 70, 443–459. [CrossRef]

3. Sklar, C.A.; Mertens, A.C.; Miltby, P.; Whitton, J.; Stovall, M.; Kasper, C.; Mulder, J.; Green, D.; Nicholson, H.S.; Yasui, Y.; et al. Premature menopause in survivors of childhood cancer: A report from the childhood cancer survivor study. J. Natl. Cancer Inst. 2006, 98, 890–896. [CrossRef] [PubMed]

4. Lee, S.; Ozkavukcu, S.; Heytens, E.; Moy, F.; Oktay, K. Value of early referral to fertility preservation in young women with breast cancer. J. Clin. Oncol. 2010, 28, 4683–4686. [CrossRef] [PubMed]

5. Lee, S.; Heytens, E.; Moy, F.; Ozkavukcu, S.; Oktay, K. Determinants of access to fertility preservation in women with breast cancer. Fertil. Steril. 2011, 95, 1932–1936. [CrossRef] [PubMed]

6. Letourneau, J.M.; Ebbel, E.E.; Katz, P.P.; Oktay, K.H.; McCulloch, C.E.; Ai, W.Z.; Chien, A.J.; Melisko, M.E.; Cedars, M.I.; Rosen, M.P. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. Cancer 2012, 118, 1933–1939. [CrossRef]

7. Kim, S.; Kim, S.W.; Han, S.J.; Lee, S.; Park, H.T.; Song, J.Y.; Kim, T. Molecular Mechanism and Prevention Strategy of Chemotherapy- and Radiotherapy-Induced Ovarian Damage. Int. J. Mol. Sci. 2021, 22, 7484. [CrossRef]

8. Bedoschi, G.; Navarro, P.A.; Oktay, K. Chemotherapy-induced damage to ovary: Mechanisms and clinical impact. Future Oncol. 2016, 12, 2333–2344. [CrossRef]

9. Wallace, W.H.; Kelsey, T.W. Human ovarian reserve from conception to the menopause. PLoS ONE 2010, 5, e8772. [CrossRef]

10. Hirshfield, A.N. Development of follicles in the mammalian ovary. Int. Rev. Cytol. 1991, 124, 43–101. [CrossRef]

11. Pepling, M.E. Follicular assembly: Mechanisms of action. Reproduction 2012, 143, 139–149. [CrossRef]

12. Skinner, M.K. Regulation of primordial follicle assembly and development. Hum. Reprod. Update 2005, 11, 461–471. [CrossRef] [PubMed]

13. Fortuno, C.; Labarta, E. Genetics of primary ovarian insufficiency: A review. J. Assist. Reprod. Genet. 2014, 31, 1573–1585. [CrossRef] [PubMed]

14. Jiao, X.; Ke, H.; Qin, Y.; Chen, Z.J. Molecular Genetics of Premature Ovarian Insufficiency. Trends Endocrinol. Metab. 2018, 29, 795–807. [CrossRef] [PubMed]

15. Pelosi, E.; Forabosco, A.; Schlessinger, D. Genetics of the ovarian reserve. Front. Genet. 2015, 6, 308. [CrossRef] [PubMed]

16. Lawson, K.A.; Dunn, N.R.; Roelen, B.A.; Zeinstra, L.M.; Davis, A.M.; Wright, C.V.; Korving, J.P.; Hogan, B.L. Bmp4 is required for proper chromosome synapsis in male and female meiosis. Trends Endocrinol. Metab. 2014, 25, 43–51. [CrossRef] [PubMed]

17. Ying, Y.; Liu, X.-M.; Marble, A.; Lawson, K.A.; Zhao, G.-Q. Requirement of Bmp8b for the generation of primordial germ cells in the mouse. Mol. Endocrinol. 2000, 14, 1053–1063. [CrossRef] [PubMed]

18. Chang, H.; Matzuk, M.M. Smad5 is required for mouse primordial germ cell development. Mech. Dev. 2001, 104, 61–67. [CrossRef] [PubMed]

19. Ying, Y.; Zhao, G.Q. Cooperation of endoderm-derived BMP2 and extraembryonic ectoderm-derived BMP4 in primordial germ cell generation in the mouse. Dev. Biol. 2001, 232, 484–492. [CrossRef] [PubMed]

20. Tremblay, K.D.; Dunn, N.R.; Robertson, E.J. Mouse embryos lacking Smad1 signals display defects in extra-embryonic tissues and germ cell formation. Development 2001, 128, 3609–3621. [CrossRef] [PubMed]

21. Nichols, J.; Zevnik, B.; Anastassiadis, K.; Niwa, H.; Koo, Y.; Chambers, I.; Scholer, H.; Smith, A. Formation of pluripotent stem cells in the mammalian embryo depends on the POU transcription factor Oct4. Cell 1998, 95, 379–391. [CrossRef] [PubMed]

22. Kobayashi, S.; Yamada, M.; Asaoka, M.; Kitamura, T. Essential role of the posterior morphogen nanos for germline development in Drosophila. Nature 1996, 380, 708–711. [CrossRef] [PubMed]

23. Tsuda, M.; Sasaoka, Y.; Kiso, M.; Abe, K.; Haraguchi, S.; Kobayashi, S.; Saga, Y. Conserved role of nanos proteins in germ cell development. Science 2003, 301, 1239–1241. [CrossRef] [PubMed]

24. Agoulnik, A.I.; Lu, B.; Zhu, Q.; Truong, C.; Ty, M.T.; Arango, N.; Chada, K.K.; Bishop, C.E. A novel gene, Pog, is necessary for primordial germ cell formation in the mouse and underlies the germ cell deficient mutation, gcd. Hum. Mol. Genet. 2002, 11, 3047–3053. [CrossRef] [PubMed]

25. Atchison, F.W.; Capel, B.; Means, A.R. Pin1 regulates the timing of mammalian primordial germ cell proliferation. Development 2003, 130, 3579–3586. [CrossRef] [PubMed]

26. Thomas, F.H.; Vanderhyden, B.C. Oocyte-granulosa cell interactions during mouse follicle development: Regulation of kit ligand expression and its role in oocyte pre-antral. Reprod. Biol. Endocrinol. 2006, 4, 19. [CrossRef] [PubMed]

27. Gavrilik, T.R.; Hale, A.N.; Flaws, J.A.; Dillon, C.P.; Green, D.R.; Rucker, E.B., 3rd. Autophagy is a cell survival program for female germ cells in the murine ovary. Reproduction 2011, 141, 759–765. [CrossRef] [PubMed]

28. Juneja, S.C.; Barr, K.J.; Enders, G.C.; Kidder, G.M. Defects in the germ line and gonads of mice lacking connexin43. Biol. Reprod. 1999, 60, 1263–1270. [CrossRef] [PubMed]

29. Romanienko, P.J.; Camerini-Otero, R.D. The mouse Spo11 gene is required for meiotic chromosome synapsis. Mol. Cell 2000, 6, 975–987. [CrossRef] [PubMed]

30. De Vries, S.S.; Baart, E.B.; Dekker, M.; Siezen, A.; de Rooij, D.G.; de Boer, P.; te Riele, H. Mouse MutS-like protein Msh5 is required for proper chromosome synapsis in male and female meiosis. Genes Dev. 1999, 13, 523–531. [CrossRef] [PubMed]

31. Knietz, B.; Cohen, P.E.; Avdievich, E.; Zhu, L.; Kane, M.F.; Hou, H.; Kolodner, R.D.; Kucherlapati, R.; Pollard, J.W.; Edelmann, W. MutS homolog 4 localization to meiotic chromosomes is required for chromosome pairing during meiosis in male and female mice. Genes Dev. 2000, 14, 1085–1097. [PubMed]
32. Pittman, D.L.; Cobb, J.; Schimenti, K.J.; Wilson, L.A.; Cooper, D.M.; Briguglio, E.; Handel, M.A.; Schimenti, J.C. Meiotic prophase arrest with failure of chromosome synopsis in mice deficient for Dmc1, a germ-line-specific RecA homolog. Mol. Cell 1998, 1, 697–705. [CrossRef]
33. Barlow, C.; Liyanage, M.; Moens, P.B.; Tarsounas, M.; Nagashima, K.; Brown, K.; Rottinghaus, S.; Jackson, S.P.; Tagle, D.; Ried, T. Atm deficiency results in severe meiotic disruption as early as leptonema of prophase I. Development 1998, 125, 4007–4017. [CrossRef] [PubMed]
34. Oktay, K.; Kim, J.Y.; Barad, D.; Babayev, S.N. Association of BRCA1 mutations with occult primary ovarian insufficiency: A possible explanation for the link between infertility and breast/ovarian cancer risks. J. Clin. Oncol. 2010, 28, 240. [CrossRef] [PubMed]
35. Lin, W.T.; Beattie, M.; Chen, L.M.; Oktay, K.; Crawford, S.L.; Gold, E.B.; Cedars, M.; Rosen, M. Comparison of age at natural menopause in BRCA1/2 mutation carriers with a non–clinic–based sample of women in northern California. Cancer 2013, 119, 1652–1659. [CrossRef] [PubMed]
36. Xu, H.; Beasley, M.D.; Warren, W.D.; van der Horst, G.T.; McKay, M.J. Absence of mouse REC8 cohesin promotes synopsis of sister chromatids in meiosis. Dev. Cell 2005, 8, 949–961. [CrossRef] [PubMed]
37. Tay, J.; Richter, J.D. Germ cell differentiation and synaptonemal complex formation are disrupted in CPEB knockout mice. Dev. Cell 2001, 1, 201–213. [CrossRef]
38. Ortega, S.; Prieto, I.; Odajima, J.; Martín, A.; Dubus, P.; Sotillo, R.; Barbero, J.L.; Malumbres, M.; Barbacid, M. Cyclin-dependent kinase 2 is essential for meiosis but not for mitotic cell division in mice. Nat. Genet. 2003, 35, 25–31. [CrossRef]
39. Fu, C.; Begum, K.; Overbeek, P.A. Primary Ovarian Insufficiency Induced by Fanconi Anemia E Mutation in a Mouse Model. PLoS ONE 2016, 11, e0144285. [CrossRef]
40. Koomen, M.; Cheng, N.C.; van de Vrugt, H.J.; Godthelp, B.C.; van der Valk, M.A.; Oostra, A.B.; Zdzienicka, M.Z.; Joenje, H.; Arwert. F. Reduced fertility and hypersensitivity to mitomycin C characterize Fancg/Xrc9 null mice. Hum. Mol. Genet. 2002, 11, 273–281. [CrossRef]
41. Whitney, M.A.; Royle, G.; Low, M.J.; Kelly, M.A.; Axthelm, M.K.; Reifsteck, C.; Olson, S.; Braun, R.E.; Heinrich, M.C.; Rathbun, R.K. Germ cell defects and hematopoietic hypersensitivity to gamma-interferon in mice with a targeted disruption of the Fanconia anemia C gene. Blood 1996, 88, 49–58. [CrossRef]
42. Cheng, N.C.; van de Vrugt, H.J.; van der Valk, M.A.; Oostra, A.B.; Krümpenfort, P.; de Vries, Y.; Joenje, H.; Berns, A.; Arwert, F. Mice with a targeted disruption of the Fanconi anemia homolog Fanca. Hum. Mol. Genet. 2000, 9, 1805–1811. [CrossRef] [PubMed]
43. Metchat, A.; Åkerfelt, M.; Bierkamp, C.; Delsinne, V.; Sistonen, L.; Alexandre, H.; Christians, E.S. Mammalian heat shock factor 1 is essential for oocyte meiosis and directly regulates Hsp90α expression. J. Biol. Chem. 2009, 284, 9521–9528. [CrossRef]
44. Bierkamp, C.; Luxey, M.; Metchat, A.; Audouard, C.; Dumollard, R.; Christians, E. Lack of maternal Heat Shock Factor 1 results in multiple cellular and developmental defects, including mitochondrial damage and altered redox homeostasis, and leads to reduced survival of mammalian oocytes and embryos. Dev. Biol. 2010, 339, 338–353. [CrossRef] [PubMed]
45. De Vries, L.; Behar, D.M.; Smirin-Yosef, P.; Lagovsky, I.; Tzur, S.; Basel-Vanagaite, L. Exome sequencing reveals SYCE1 mutation associated with autosomal recessive primary ovarian insufficiency. J. Clin. Endocrinol. Metab. 2014, 99, E2129–E2132. [CrossRef]
46. Lacombe, A.; Lee, H.; Zahed, L.; Choucair, M.; Muller, J.-M.; Nelson, S.F.; Salameh, W.; Vilain, E. Disruption of POF1B binding to nonmuscle actin filaments is associated with premature ovarian failure. Am. J. Hum. Genet. 2006, 79, 113–119. [CrossRef] [PubMed]
47. Wang, J.; Zhang, W.; Jiang, H.; Wu, B.-L. Mutations in HFM1 in recessive primary ovarian insufficiency. Hum. Mol. Genet. 2014, 23, 972–974. [CrossRef]
48. Caburet, S.; Arboleda, V.A.; Llano, E.; Overbeek, P.A.; Barbero, J.L.; Oka, K.; Harrison, W.; Vaiman, D.; Ben-Neriah, Z.; Garcia-Tunón, I. Mutant cohesin in premature ovarian failure. N. Engl. J. Med. 2014, 370, 943–949. [CrossRef] [PubMed]
49. Soyal, S.M.; Amleh, A.; Dean, J. FlIgalpha, a germ cell-specific transcription factor required for ovarian follicle formation. Development 2000, 127, 4645–4654. [CrossRef] [PubMed]
50. Zhao, H.; Chen, Z.-J.; Qin, Y.; Shi, Y.; Wang, S.; Choi, Y.; Simpson, J.L.; Rajkovic, A. Transcription factor FIGLA is mutated in patients with premature ovarian failure. Am. J. Hum. Genet. 2008, 82, 1342–1348. [CrossRef] [PubMed]
51. Kerr, B.; García-Rudaz, C.; Dorfman, M.; Paredes, A.; Ojeda, S.R. NTRK1 and NTRK2 receptors facilitate follicle assembly and early follicular development in the mouse ovary. Reproduction 2009, 138, 131–140. [CrossRef] [PubMed]
52. Spears, N.; Molinek, M.D.; Robinson, L.L.; Fulton, N.; Cameron, H.; Shimoda, K.; Telfer, E.E.; Anderson, R.A.; Price, D.J. The role of neurotrophin receptors in female germ-cell survival in mouse and human. Development 2003, 130, 5481–5491. [CrossRef] [PubMed]
53. Nilsson, E.; Dole, G.; Skinner, M.K. Neurotrophin NT3 promotes ovarian primordial to primary follicle transition. Reprod. Camb. Endocrinol. 2009, 138, 697.
54. Bergeron, L.; Perez, G.I.; Macdonald, G.; Shi, L.; Sun, Y.; Jurisicova, A.; Varmuza, S.; Latham, K.E.; Flaws, J.A.; Salter, J.C. Defects in regulation of apoptosis in caspase-2-deficient mice. Genes Dev. 1998, 12, 1304–1314. [CrossRef]
55. Ratts, V.S.; Flaws, J.A.; Kolp, R.; Sorenson, C.M.; Tilly, J.L. Ablation of bel-2 gene expression decreases the numbers of oocytes and primordial follicles established in the post-natal female mouse gonad. Endocrinology 1995, 136, 3665–3668. [CrossRef]
56. Greenfeld, C.R.; Pepling, M.E.; Babus, J.K.; Furth, P.A.; Flaws, J.A. BAX regulates follicular endowment in mice. Reproduction 2007, 133, 865–876. [CrossRef]
57. Perez, G.I.; Robles, R.; Knudson, C.M.; Flaws, J.A.; Korsmeyer, S.J.; Tilly, J.L. Prolongation of ovarian lifespan in advanced chronological age by Bax-deficiency. *Nat. Genet.* 1999, 21, 200–203. [CrossRef]

58. Benedict, J.C.; Lin, T.-M.; Loeffler, I.; Peterson, R.E.; Flaws, J.A. Physiological role of the aryl hydrocarbon receptor in mouse ovary development. *Toxicol. Sci.* 2000, 56, 382–388. [CrossRef]

59. Omari, S.; Waters, M.; Naranian, T.; Kim, K.; Perumalsamy, A.; Chi, M.; Greenblatt, E.; Moley, K.; Opferman, J.; Jurisicova, A. McI-1 is a key regulator of the ovarian reserve. *Cell Death Dis.* 2015, 6, e1755. [CrossRef]

60. Winship, A.L.; Stringer, J.M.; Liew, S.H.; Hutt, K.J. The importance of DNA repair for maintaining oocyte quality in response to anti-cancer treatments, environmental toxins and maternal ageing. *Hum. Reprod. Update* 2018, 24, 119–134. [CrossRef]

61. Amelio, I.; Grespi, F.; Annicchiario-Petruzzelli, M.; Melino, G. p63 is the guardian of human reproduction. *Cell Cycle* 2012, 11, 4545–4551. [CrossRef]

62. Suh, E.K.; Yang, A.; Kettenbach, A.; Bamberger, C.; Michaelis, A.H.; Zhu, Z.; Elvin, J.A.; Bronson, R.T.; Crum, C.P.; McKeon, F. p63 protects the female germ line during meiotic arrest. *Nature* 2006, 444, 624–628. [CrossRef]

63. Kerr, J.B.; Hutt, K.J.; Michalak, E.M.; Cook, M.; Vandenberg, C.J.; Liew, S.H.; Bouillet, P.; Mills, A.; Scott, C.L.; Findlay, J.K.; et al. DNA damage-induced primordial follicle oocyte apoptosis and loss of fertility require TAp63-mediated induction of Puma and Noxa. *Mol. Cell* 2012, 48, 343–352. [CrossRef]

64. Soleimani, R.; Heytens, E.; Darzynkiewicz, Z.; Oktay, K. Mechanisms of chemotherapy-induced human ovarian aging: Double strand DNA breaks and microvascular compromise. *Aging* 2011, 3, 782–793. [CrossRef]

65. Roness, H.; Kashi, O.; Meirov, D. Prevention of chemotherapy-induced ovarian damage. *Fertil. Steril.* 2016, 105, 20–29. [CrossRef]

66. Chen, X.Y.; Xia, H.X.; Guan, H.Y.; Li, B.; Zhang, W. Follicle Loss and Apoptosis in Cyclophosphamide-Treated Mice: What's the Matter? *Int. J. Mol. Sci.* 2016, 17, 836. [CrossRef] [PubMed]

67. Roness, H.; Gavish, Z.; Cohen, Y.; Meirov, D. Ovarian follicle burnout: A universal phenomenon? *Cell Cycle* 2013, 12, 3245–3246. [CrossRef] [PubMed]

68. Marcello, M.F.; Nuciforo, G.; Romeo, R.; Di Dino, G.; Russo, I.; Russo, A.; Palumbo, G.; Schiliro, G. Structural and ultrastructural study of the ovary in childhood leukemia after successful treatment. *Cancer* 1990, 66, 2099–2104. [CrossRef]

69. Nicosia, S.V.; Matus-Ridley, M.; Meadows, A.T. Gonadal effects of cancer therapy in girls. *Cancer* 1985, 55, 2364–2372. [CrossRef]

70. Ben-Aharon, I.; Meizner, I.; Granot, T.; Uri, S.; Hasky, N.; Rizel, S.; Verushalmi, R.; Sulkes, A.; Stemmer, S.M. Chemotherapy-induced ovarian failure as a prototype for acute vascular toxicity. *Oncologist* 2012, 17, 1386–1393. [CrossRef]

71. Meirov, D.; Dor, J.; Kaufman, B.; Shrim, A.; Rabinovici, J.; Schiff, E.; Raanani, H.; Levin, J.; Friedman, E. Cortical fibrosis and blood-vessels damage in human ovaries exposed to chemotherapy. Potential mechanisms of ovarian injury. *Hum. Reprod.* 2007, 22, 1626–1633. [CrossRef]

72. Soleimani, R.; Heytens, E.; Oktay, K. Enhancement of neoangiogenesis and follicle survival by sphingosine-1-phosphate in human ovarian tissue xenotransplants. *PLoS ONE* 2011, 6, e19475. [CrossRef]

73. De la Noval, B.D. Potential implications on female fertility and reproductive lifespan in BRCA germline mutation women. *Arch. Gynecol. Obstet.* 2016, 294, 1099–1103. [CrossRef]

74. Titus, S.; Li, F.; Stobezki, R.; Akula, K.; Unsal, E.; Jeong, K.; Dickler, M.; Robson, M.; Moy, F.; Goswami, S. Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans. *Sci. Transl. Med.* 2013, 5, ra121–ra172. [CrossRef]

75. Michaelsson-Cohen, R.; Mor, P.; Srebnik, N.; Beller, U.; Levy-Lahad, E.; Eldar-Geva, T. BRCA mutation carriers do not have compromised ovarian reserve. *Int. J. Cancer* 2014, 24, 233–237. [CrossRef]

76. Shapira, M.; Raanani, H.; Feldman, B.; Srebnik, N.; Dereck-Haim, S.; Manela, D.; Brengmausen, M.; Geva-Lerner, L.; Friedman, E.; Levi-Lahad, E. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. *Fertil. Steril.* 2015, 104, 1162–1167. [CrossRef]

77. Lee, J.M.; Ledermann, J.A.; Kohn, E.C. PARP Inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies. *Ann. Oncol.* 2014, 25, 32–40. [CrossRef] [PubMed]

78. Kim, D.H.; Lee, H.R.; Kim, M.G.; Lee, J.S.; Jin, S.J.; Lee, H.T. The effect of poly(ADP-ribosylation) inhibition on the porcine cumulus-oocyte complex development during in vitro maturation. *Biochem. Biophys. Res. Commun.* 2017, 483, 752–758. [CrossRef] [PubMed]

79. Nakamura, K.; Take, S.; Shiraishi, E.; Shinya, K.; Iguadal, A.J.; Suzuki, N. Poly (ADP-ribose) polymerase inhibitor exposure reduces ovarian reserve followed by dysfunction in granulosa cells. *Sci. Rep.* 2020, 10, 17058. [CrossRef] [PubMed]

80. Dou, X.; Guo, T.; Li, G.; Zhou, L.; Qin, Y.; Chen, Z.J. Minichromosome maintenance complex component 8 mutations cause primary ovarian insufficiency. *Fertil. Steril.* 2016, 106, 1485–1489.e1482. [CrossRef] [PubMed]

81. Xiao, W.J.; He, W.B.; Zhang, Y.X.; Meng, L.L.; Lu, G.X.; Lin, G.; Tan, Y.Q.; Du, J. In-Frame Variants in STAG3 Gene Cause Premature Ovarian Insufficiency. *Front. Genet.* 2019, 10, 1016. [CrossRef]

82. Weinberg-Shukron, A.; Renbaum, P.; Kalifa, R.; Zeligson, S.; Ben-Neriah, Z.; Dreiffuss, A.; Abu-Rayyan, A.; Maatuk, N.; Fardian, N.; Reker, D.; et al. A mutation in the nucleoporin-107 gene causes XX gonadal dysgenesis. *J. Clin. Investig.* 2015, 125, 4295–4304. [CrossRef] [PubMed]

83. Zhe, J.; Chen, S.; Chen, X.; Liu, Y.; Li, Y.; Zhou, X.; Zhang, J. A novel heterozygous splice-altering mutation in HFM1 may be a cause of premature ovarian insufficiency. *J. Ovarian Res.* 2019, 12, 61. [CrossRef] [PubMed]

84. Wu, X.; Wang, B.; Dong, Z.; Zhou, S.; Liu, Z.; Shi, G.; Cao, Y.; Xu, Y. A NANOS3 mutation linked to protein degradation causes premature ovarian insufficiency. *Cell Death Dis.* 2013, 4, e825. [CrossRef] [PubMed]
85. Franca, M.M.; Mendonca, B.B. Genetics of Primary Ovarian Insufficiency in the Next-Generation Sequencing Era. *J. Endocr. Soc.* 2020, 4, bv2037. [CrossRef] [PubMed]

86. Mansouri, M.R.; Schuster, J.; Badhai, J.; Stattin, E.L.; Losel, R.; Wehling, M.; Carlsson, B.; Hovatta, O.; Karlstrom, P.O.; Golovleva, I.; et al. Alterations in the expression, structure and function of progesterone receptor membrane component-1 (PGRMC1) in premature ovarian failure. *Hum. Mol. Genet.* 2008, 17, 3776–3783. [CrossRef]

87. Castrillon, D.H.; Miao, L.; Kollipara, R.; Horner, J.W.; DePinho, R.A. Suppression of ovarian follicle activation in mice by the transcription factor Foxo3a. *Science* 2003, 301, 215–218. [CrossRef]

88. Watkins, W.J.; Umbers, A.J.; Wood, K.J.; Harris, S.E.; Winship, I.M.; Gersak, K.; Shelling, A.N. Mutational screening of FOXO3A and FOXO1A in women with premature ovarian failure. *Fertil. Steril.* 2006, 86, 1518–1521. [CrossRef]

89. Wang, B.; Mu, Y.; Ni, F.; Zhou, S.; Wang, J.; Cao, Y.; Ma, X. Analysis of FOXO3 mutation in 114 Chinese women with premature ovarian failure. *Reprod. Biomed. Online* 2010, 20, 499–503. [CrossRef]

90. Woad, K.J.; Pearson, S.M.; Harris, S.E.; Gersak, K.; Shelling, A.N. Investigating the association between inhibin alpha gene promoter polymorphisms and premature ovarian failure. *Fertil. Steril.* 2009, 91, 62–66. [CrossRef]

91. Corre, T.; Schuettler, J.; Bione, S.; Marozzi, A.; Persani, L.; Rossetti, R.; Torricelli, F.; Giotti, I.; Vogt, P.; Toniolo, D. A large-scale association study to assess the impact of known variants of the human INHA gene on premature ovarian failure. *Hum. Reprod.* 2009, 24, 2023–2028. [CrossRef]

92. Al-ajoury, R.; Kassem, E.; Al-halabi, B.; Moassess, F.; Al-achkar, W. Investigation of some genetic variations in BMP15 accompanied with premature ovarian failure (POF) in Syrian women. *Middle East Fertil. Soc. J.* 2015, 20, 91–96. [CrossRef]

93. Cho, H.W.; Lee, S.; Min, K.J.; Hong, J.H.; Song, J.Y.; Lee, J.K.; Lee, N.W.; Kim, T. Advances in the Treatment and Prevention of Chemotherapy-Induced Ovarian Toxicity. *Int. J. Mol. Sci.* 2020, 21, 7792. [CrossRef]

94. Jiang, Y.; Zhang, Z.; Cha, L.; Li, L.; Zhu, D.; Fang, Z.; He, Z.; Huang, J.; Pan, Z. Resveratrol Plays a Protective Role against Premature Ovarian Failure and Prompts Female Germline Stem Cell Survival. *Int. J. Mol. Sci.* 2019, 20, 3605. [CrossRef] [PubMed]

95. Sun, B.; Yeh, J. Onco-fertility and personalized testing for potential for loss of ovarian reserve in patients undergoing chemotherapy. *Fertil. Res. Pract.* 2021, 7, 13. [CrossRef] [PubMed]

96. Barzon, L.; Lavezzo, E.; Miliotello, V.; Toppo, S.; Palu, G. Applications of next-generation sequencing technologies to diagnostic virology. *Int. J. Mol. Sci.* 2011, 12, 7861–7884. [CrossRef]

97. Blumenfeld, Z.; Dann, E. GnRH agonist for the prevention of chemotherapy-induced ovarian failure in lymphoma. *J. Clin. Oncol.* 2013, 31, 3721. [CrossRef]

98. Blumenfeld, Z.; Avivi, I.; Linn, S.; Epelbaum, R.; Ben-Shahar, M.; Haim, N. Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy. *Hum. Reprod. 1996, 11*, 1620–1626. [CrossRef]

99. Pereyra Pacheco, B.; Mendez Ribas, J.M.; Milone, G.; Fernandez, I.; Kvicala, R.; Mila, T.; Di Noto, A.; Contreras Ortiz, O.; Pavlovsky, S. Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: A preliminary report. *Gynecol. Oncol. 2001, 81*, 391–397. [CrossRef]

100. Recchia, F.; Sica, G.; De Filippis, S.; Saggio, G.; Rosselli, M.; Rea, S. Goserelin as ovarian protection in the adjuvant treatment of premenopausal breast cancer: A phase II pilot study. *Anticancer Drugs* 2002, 13, 417–424. [CrossRef]

101. Blumenfeld, Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in toxicity in young women by GnRH-a. *J. Natl. Cancer Inst. Monogr.* 2005, 34, 40–43. [CrossRef] [PubMed]

102. Blumenfeld, Z.; Eckman, A. Preservation of fertility and ovarian function and minimization of chemotherapy-induced gonado-toxicity in young women by GnRH-a. *J. Natl. Cancer Inst. Monogr.* 2009, 2023–2028. [CrossRef]

103. Lambertini, M.; Horicks, F.; Del Mastro, L.; Partridge, A.H.; Demeestere, I. Ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy in cancer patients: From biological evidence to clinical application. *Cancer Treat. Rev.* 2019, 72, 65–77. [CrossRef] [PubMed]

104. De Pedro, M.; Otero, B.; Martin, B. Fertility preservation and breast cancer: A review. *Ecancermedicalscience* 2015, 9, 503. [CrossRef]

105. Kalechman, Y.; Albeck, M.; Oron, M.; Sobelman, D.; Gurwith, M.; Horwith, G.; Kirsch, T.; Maida, B.; Sehgal, S.N.; Sredni, B. Protective and restorative role of AS101 in combination with chemotherapy. *Cancer Res.* 1991, 51, 1499–1503. [CrossRef]

106. Makarovsky, D.; Kalechman, Y.; Sonino, T.; Freidkin, I.; Teitz, S.; Albeck, M.; Weil, M.; Gefen-Aricha, R.; Yadid, G.; Sredni, B. Tellurium compound AS101 induces PC12 differentiation and rescues the neurons from apoptotic death. *Ann. N. Y. Acad. Sci.* 2003, 1010, 659–666. [CrossRef] [PubMed]

107. Kalich-Philosoph, L.; Roness, H.; Carmely, A.; Fishel-Bartal, M.; Liguimsky, H.; Paglin, S.; Wolf, I.; Kanety, H.; Sredni, B.; Meirow, D. Cyclophosphamide triggers follicle activation and “burnout”; AS101 prevents follicle loss and preserves fertility. *Sci. Transl. Med.* 2013, 5, 185ra162. [CrossRef]

108. Duker, B.J.; Tamura, S.; Buchdunger, E.; Ohno, S.; Segal, G.M.; Fanning, S.; Zimmermann, J.; Lydon, N.B. Effects of a selective inhibitor of the aB1 tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat. Med.* 1996, 2, 561–566. [CrossRef]

109. Gonfloni, S.; Di Tella, L.; Caldarola, S.; Cannata, S.M.; Klenger, F.G.; Di Bartolomeo, C.; Mattei, M.; Candi, E.; De Felici, M.; Melino, G.; et al. Inhibition of the aB1-TPA pathway protects mouse oocytes from chemotherapy-induced death. *Nat. Med.* 2009, 15, 1179–1185. [CrossRef] [PubMed]
110. Kerr, J.B.; Hutt, K.J.; Cook, M.; Speed, T.P.; Strasser, A.; Findlay, J.K.; Scott, C.L. Cisplatin-induced primordial follicle oocyte killing and loss of fertility are not prevented by imatinib. Nat. Med. 2012, 18, 1172–1174. [CrossRef]

111. Kim, S.Y.; Cordeiro, M.H.; Serna, V.A.; Ebbert, K.; Butler, L.M.; Sinha, S.; Mills, A.A.; Woodruff, T.K.; Kurita, T. Rescue of platinum-damaged oocytes from programmed cell death through inactivation of the p53 family signaling network. Cell Death Differ. 2013, 20, 987–997. [CrossRef] [PubMed]

112. Morgan, S.; Lopes, F.; Gourley, C.; Anderson, R.A.; Spears, N. Cisplatin and doxorubicin induce distinct mechanisms of ovarian follicle loss; imatinib provides selective protection only against cisplatin. PLoS ONE 2013, 8, e70117. [CrossRef]

113. Morita, Y.; Perez, G.I.; Paris, F.; Miranda, S.R.; Ehleiter, D.; Haimovitz-Friedman, A.; Fuku, Z.; Xie, Z.; Reed, J.C.; Schuchman, E.H.; et al. Oocyte apoptosis is suppressed by disruption of the acid sphingomyelinase gene or by sphingosine-1-phosphate therapy. Nat. Med. 2000, 6, 1109–1114. [CrossRef]

114. Li, F.; Turan, V.; Lieman, S.; Cuvelier, C.; De Sutter, P.; Oktay, K. Sphingosine-1-phosphate prevents chemotherapy-induced human primordial follicle death. Hum. Reprod. 2014, 29, 107–113. [CrossRef]

115. Hancke, K.; Strauch, O.; Kissel, C.; Gobel, H.; Schafer, W.; Denschlag, D. Sphingosine 1-phosphate protects ovaries from chemotherapy-induced damage in vivo. Fertil. Steril. 2007, 87, 172–177. [CrossRef] [PubMed]

116. Kaya, H.; Desdicioglu, R.; Sezik, M.; Ulukaya, E.; Ozkaya, O.; Yilmaztepe, A.; Demirci, M. Does sphingosine-1-phosphate have a protective effect on cyclophosphamide- and irradiation-induced ovarian damage in the rat model? Fertil. Steril. 2008, 89, 732–735. [CrossRef]

117. Gook, D.A.; Edgar, D.H. Human oocyte cryopreservation. Hum. Reprod. Update 2007, 13, 591–605. [CrossRef]

118. Lee, S.; Song, J.Y.; Ku, S.Y.; Kim, S.H.; Kim, T. Fertility preservation in women with cancer. Clin. Exp. Reprod. Med. 2012, 39, 46–51. [CrossRef] [PubMed]

119. Rienzi, L.; Gracia, C.; Maggilli, R.; LaBarbera, A.R.; Kaser, D.J.; Ubaldi, F.M.; Vanderpoel, S.; Racowsky, C. Oocyte, embryo and blastocyst cryopreservation in ART: Systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum. Reprod. Update 2017, 23, 139–155. [CrossRef] [PubMed]

120. AbdellHafez, F.F.; Desal, N.; Abou-Setta, A.M.; Falcone, T.; Goldfarb, J. Slow freezing, vitrification and ultra-rapid freezing of human embryos: A systematic review and meta-analysis. Reprod. Biomed. Online 2010, 20, 209–222. [CrossRef]

121. Debrook, S.; Peerka, K.; Fernandez Gallardo, E.; De Neubourg, D.; Spiessens, C.; D’Hooghe, T.M. Vitrification of cleavage stage day 3 embryos results in higher live birth rates than conventional slow freezing: A RCT. Hum. Reprod. 2015, 30, 1820–1830. [CrossRef]

122. Oktay, K.; Cil, A.P.; Bang, H. Efficiency of oocyte cryopreservation: A meta-analysis. Fertil. Steril. 2006, 86, 70–80. [CrossRef]

123. Dolmans, M.M.; Hollander de Ouderaen, S.; Demydle, D.; Pirard, C. Utilization rates and results of long-term embryo cryopreservation before gonadotoxic treatment. J. Assist. Reprod. Genet. 2015, 32, 1233–1237. [CrossRef]

124. Courbiere, B.; Decanter, C.; Bringer-Deutsch, S.; Rives, N.; Mirallie, S.; Pech, J.C.; De Ziegler, D.; Carre-Pigeon, F.; May-Panloup, P.; Sifer, C.; et al. Emergency IVF for embryo freezing to preserve female fertility: A French multicentre cohort study. Hum. Reprod. 2013, 28, 2381–2388. [CrossRef]

125. Mayeur, A.; Puy, V.; Windal, V.; Hesters, L.; Gallot, V.; Benoit, A.; Grynberg, M.; Sonigo, C.; Frydman, N. Live birth rate after use of cryopreserved oocytes or embryos at the time of cancer diagnosis in female survivors: A retrospective study of ten years of experience. J. Assist. Reprod. Genet. 2021, 38, 1767–1775. [CrossRef]

126. Kim, S.; Lee, Y.; Lee, S.; Kim, T. Ovarian tissue cryopreservation and transplantation in patients with cancer. Obstet. Gynecol. Sci. 2018, 61, 431–442. [CrossRef] [PubMed]

127. Cobo, A.; Garcia-Velasco, J.A.; Domingo, J.; Remohi, J.; Pellicer, A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil. Steril. 2013, 99, 1485–1495. [CrossRef]

128. Cobo, A.; Diaz, C. Clinical application of oocyte vitrification: A systematic review and meta-analysis of randomized controlled trials. Fertil. Steril. 2011, 96, 277–285. [CrossRef]

129. Ubaldi, F.; Anniballo, R.; Romano, S.; Baroni, E.; Albirici, L.; Colamaria, S.; Capalbo, A.; Sapienza, F.; Vajta, G.; Rienzi, L. Cumulative ongoing pregnancy rate achieved with oocyte vitrification and cleavage stage transfer without embryo selection in a standard infertility program. Hum. Reprod. 2010, 25, 1199–1205. [CrossRef] [PubMed]

130. Rienzi, L.; Romano, S.; Albirici, L.; Maggilli, R.; Capalbo, A.; Baroni, E.; Colamaria, S.; Ubaldi, F. Embryo development of fresh ‘versus’ vitrified metaphase II oocytes after ICSI: A prospective randomized sibling-oocyte study. Hum. Reprod. 2010, 25, 66–73. [CrossRef] [PubMed]

131. Dittrich, R.; Lotz, L.; Mueller, A.; Hoffmann, I.; Wachter, D.L.; Amann, K.U.; Beckmann, M.W.; Hildebrandt, T. Oncofertility: Combination of ovarian stimulation with subsequent ovarian tissue extraction on the day of oocyte retrieval. Reprod. Biol. Endocrinol. 2013, 11, 19. [CrossRef]

132. Suzuki, N. Ovarian tissue cryopreservation in young cancer patients for fertility preservation. Reprod. Med. Biol. 2015, 14, 1–4. [CrossRef]

133. Lee, S.; Ryu, K.J.; Kim, B.; Kang, D.; Kim, Y.Y.; Kim, T. Comparison between Slow Freezing and Vitrification for Human Ovarian Tissue Cryopreservation and Xenotransplantation. Int. J. Mol. Sci. 2019, 20, 3346. [CrossRef]

134. Donnez, J.; Dolmans, M.M.; Pellicer, A.; Diaz-Garcia, C.; Sanchez Serrano, M.; Schmidt, K.T.; Ernst, E.; Luyckx, V.; Andersen, C.Y. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: A review of 60 cases of reimplantation. Fertil. Steril. 2013, 99, 1503–1513. [CrossRef] [PubMed]
135. Dolmans, M.M.; Luyckx, V.; Donnez, J.; Andersen, C.Y.; Greve, T. Risk of transferring malignant cells with transplanted frozen-thawed ovarian tissue. Fertil. Steril. 2013, 99, 1514–1522. [CrossRef] [PubMed]

136. Loren, A.W.; Senapati, S. Fertility preservation in patients with hematologic malignancies and recipients of hematopoietic cell transplants. Blood 2019, 134, 746–760. [CrossRef] [PubMed]

137. Bedaiwy, M.A.; Falcone, T. Ovarian tissue banking for cancer patients: Reduction of post-transplantation ischaemic injury: Intact ovary freezing and transplantation. Hum. Reprod. 2004, 19, 1242–1244. [CrossRef] [PubMed]

138. Martinez-Madrid, B.; Dolmans, M.M.; Van Langendonckt, A.; Defrere, S.; Donnez, J. Freeze-thawing intact human ovary with its vascular pedicle with a passive cooling device. Fertil. Steril. 2004, 82, 1390–1394. [CrossRef] [PubMed]

139. Yin, H.; Wang, X.; Kim, S.S.; Chen, H.; Tan, S.L.; Gosden, R.G. Transplantation of intact rat gonads using vascular anastomosis: Effects of cryopreservation, ischaemia and genotype. Hum. Reprod. 2003, 18, 1165–1172. [CrossRef]

140. Zhang, J.M.; Sheng, Y.; Cao, Y.Z.; Wang, H.Y.; Chen, Z.J. Cryopreservation of whole ovaries with vascular pedicles: Vitrification or conventional freezing? J. Assist. Reprod. Genet. 2011, 28, 445–452. [CrossRef]

141. Zhang, S.; Yao, H.; Liu, Y.; Ren, L.; Xiang, D.; Wang, Y. Hypothermic machine perfusion after static cold storage improves ovarian function in rat ovarian tissue transplantation. J. Assist. Reprod. Genet. 2020, 37, 1745–1753. [CrossRef]

142. Hossay, C.; Donnez, J.; Dolmans, M.M. Whole Ovary Cryopreservation and Transplantation: A Systematic Review of Challenges and Research Developments in Animal Experiments and Humans. J. Clin. Med. 2020, 9, 3196. [CrossRef]

143. Lee, J.A.; Barritt, J.; Moschini, R.M.; Slifkin, R.E.; Copperman, A.B. Optimizing human oocyte cryopreservation for fertility preservation patients: Should we mature then freeze or freeze then mature? Fertil. Steril. 2013, 99, 1356–1362. [CrossRef] [PubMed]

144. Son, W.Y.; Henderson, S.; Cohen, Y.; Dahan, M.; Buckett, W. Immature Oocyte for Fertility Preservation. Front. Endocrinol. 2019, 10, 464. [CrossRef] [PubMed]

145. Prasath, E.B.; Chan, M.L.; Wong, W.H.; Lim, C.J.; Tharmalingam, M.D.; Hendricks, M.; Loh, S.F.; Chia, Y.N. First pregnancy and live birth resulting from cryopreserved embryos obtained from in vitro matured oocytes after oophorectomy in an ovarian cancer patient. Hum. Reprod. 2014, 29, 276–278. [CrossRef] [PubMed]

146. Uzelac, P.S.; Delaney, A.A.; Christensen, G.L.; Bohler, H.C.; Nakajima, S.T. Live birth following in vitro maturation of oocytes retrieved from extracorporeal ovarian tissue aspiration and embryo cryopreservation for 5 years. Fertil. Steril. 2015, 104, 1258–1260. [CrossRef]

147. Cho, E.; Kim, Y.Y.; Nob, K.; Ku, S.Y. A new possibility in fertility preservation: The artificial ovary. J. Tissue Eng. Regen. Med. 2019, 13, 1294–1315. [CrossRef]

148. Luyckx, V.; Dolmans, M.M.; Vanacker, J.; Legat, C.; Fortuno Moya, C.; Donnez, J.; Amorim, C.A. A new step toward the artificial ovary: Survival and proliferation of isolated murine follicles after autologous transplantation in a fibrin scaffold. Fertil. Steril. 2014, 101, 1149–1156. [CrossRef]

149. Vanacker, J.; Luyckx, V.; Dolmans, M.M.; Des Rieux, A.; Jaeger, J.; Van Langendonckt, A.; Donnez, J.; Amorim, C.A. Transplantation of an alginate-matrigel matrix containing isolated ovarian cells: First step in developing a biodegradable scaffold to transplant isolated preantral follicles and ovarian cells. Biomaterials 2012, 33, 6079–6085. [CrossRef]

150. Johnson, J.; Canning, J.; Kaneko, T.; Pru, J.K.; Tilly, J.L. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 2004, 428, 145–150. [CrossRef]

151. Tilly, J.L.; Telfer, E.E. Purification of germline stem cells from adult mammalian ovaries: A step closer towards control of the female biological clock? Mol. Hum. Reprod. 2009, 15, 393–398. [CrossRef] [PubMed]

152. Hutt, K.J.; Albertini, D.F. Clinical applications and limitations of current ovarian stem cell research: A review. J. Exp. Clin. Assist. Reprod 2006, 3, 6. [CrossRef] [PubMed]