Clinics in Cancer Research and Reports

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The Controversy Regarding Association of Naturally Decreased Amh Quantities in Young Women Who Generate Cancer Still Persists: A Short Communication

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Received: December 28, 2022 | **Accepted:** January 13, 2023 | **Published:** February 10, 2023
Citation: DR Kulvinder Kochar Kaur, DR Gautam Nand K Allahbadia, DR Mandeep Singh. The Controversy Regarding Association of Naturally Decreased Amh Quantities in Young Women Who Generate Cancer Still Persists: A Short Communication, Clinics in Cancer Research and Reports. 1(1).

Abstract

Inspite of massive evaluation of the pathophysiological modes there is the absence of insight regarding modes of premature ovarian aging that results in diminished ovarian reserve (DOR) in addition to probably infertility in case of young women.

Keywords: Wound; tissue damage; injuries; ulcers; health

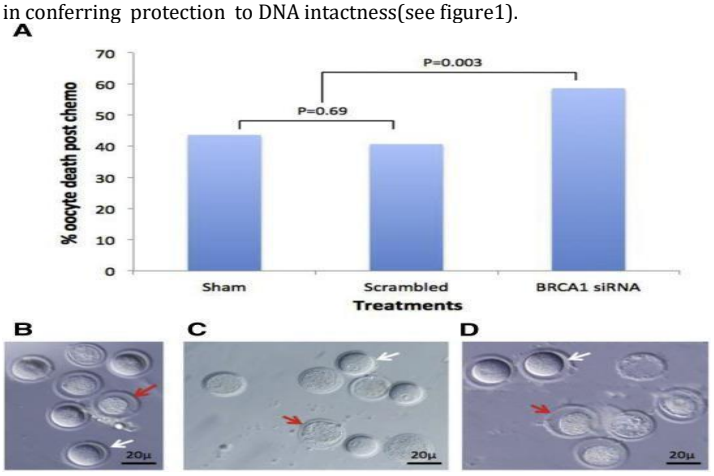
Short Communication

Inspite of massive evaluation of the pathophysiological modes there is the absence of insight regarding modes of premature ovarian aging that results in diminished ovarian reserve(DOR) in addition to probably infertility in case of young women.The well acknowledged canonical risk factors for DOR are aggravated ovarian surgery,endometriosis along with cytotoxic treatment; nevertheless, gene mutations like FregileX syndrome can further result in premature ovarian elimination of ovarian follicles as well as DOR.The BRCA1 along with BRCA2genes are crucial members of the kinase ataxia - telangiectasia mutated(ATM)- deoxy ribonucleic acid(DNA) double strand break(DSB) healing pathway. Mutations of these genes are correlated with an escalated risk of breast as well as ovarian cancer generation [1]. At the time of generation of ovarian stimulation protocols with aromatase hamper**ing** agents in women with breast cancer(BC)the group of Oktay along with others the observation was that in women with BC,the ones possessing the BRCA mutations generated lesser oocytes[2,3].

Serum antimullerian hormone (AMH) gets generated from the proliferating granulosa cells whose destruction takes place at the time of chemotherapy. Ovarian reserve is comprised of primordial follicles(PF) that are quiet,thus do not produce AMH [4]. In view of the population size of follicles that get produced have a direct association with the generating follicles[5]. Despite,no markeris perfect regarding quantification of PF in human ovary,noninvasively , AMH determination gives maximum precision for identification of injury subsequent to chemotherapy on ovarian reserve[6].In view of unpublished observations of Oktay group besides restricted work they determined that 3-6 mths might be the need for the repopulation of the generating follicles pool to AMH quantities that are determinable.Thus AMH quantities that can get determined would reach a steady state to point to the chemotherapy stimulated ovarian injury[9].To assess if BRCA mutations in contrast to those not possessing BRCA mutations would generate greater ovarian reserve loss they planned a study.

Thus despite diminished ovarian function that result in infertility is implicated in a robust psychological load on the patients impacted, outcomes pointed towards a probable association amongst gene mutations, dysfunctional DNA healing modes along with escalated risk of generation of cancer.The probably association of infertility regarding long term health along with life anticipation has been illustrated in a new publication,that detailed a 10% escalated risk of mortality in case of infertile patients with a 47% escalated risk of mortality in view of cancer][8].

Oktay etal.[9], carried out the assessment of prior cytotoxic ovarian reserve in addition to post cytotoxic therapy in case of patients possessing the BRCA mutations. Oktay etal.[9], illustrated that with great clarity that patients impacted by BRCA gene encountered a considerable reduction in antimullerian hormone (AMH) quantities along with decreased recovery subsequent to chemotherapy in contrast to non influenced women.Their observation along with prior publications of their group corroborated the same posit that DNAhealing deficiency is a common mode amongst ovarian aging, infertility along with cancer in view of both BRCA genes have the akin family of DNA double strand breaks(DSB) healing genes, possessing a key part in conferring protection to DNA intactness(see figure1).



Courtesy ref no.9-*BRCA*1 deficiency results in oocyte sensitivity to chemotherapy in a mouse bioassay. FVB mice oocytes were treated with doxorubicin (100 µg/mL) for 1 hour after sham, scrambled small interfering ribonucleic acid (siRNA), or siRNA microinjection to silence *BRCA*1 in the oocytes. Oocyte survival was assessed 8 hours later. (A) Significant increase (*P* = .003) in the percentage of oocyte death was observed in the *BRCA* silenced group (128 oocytes from 8 mice) when compared to the sham (110 oocytes from 8 mice) and scrambled-siRNA-injected group (118 oocytes from 8 mice). Representative differential interference contrast images of the sham (B), scrambled siRNA (C) and *BRCA*1 siRNA-treated (D) oocytes are shown after doxorubicin exposure. *White arrows* point to representative viable and *red arrows* point to nonviable oocytes.

DNA injury can take place secondary to endogenous as well as exogenous processes along with might take origin in various diversities.The DSBs where the phosphate backbones regarding the 2 corresponding DNA strands break at the same time,reflects the maximum cytotoxic injury . in view of genomic intactness is of considerable significance regarding cell survival along with in view of genomic injury might result in mutagenesis in addition to cancer over evolution cells have generated particular healing pathways for tackling DNA injuries,the DNA damage response (DDR).Working DDR is key for health along with subjects impacted by DDR mutations in the DDR genes can reveal variation of conditions of nervous, immune in addition to reproductive system along with being prone to premature aging as well as cancer generation[10].

DDR further possesses a key part in the formation of gametes like at the time of meiosis amongst the homologous chromosomes need interchange of genetic matter.In this such interchange the generation of DSB is implicated along with their following healing by homologous recombination. Deficiency in the healing system of DSBs at the time of meiosis might cause infertility.

The impact of mutations regarding DDR gets apparent in case of patients with Fanconi - anaemia(FA). FA reflects an autosomal recessive condition that possesses the properties of propagative bone marrow failure as well as considerably greater incidence along with proneness towards cancer generation in addition to decreased fertility amongst other congenital aberrations . Maximum of patients with FA possess significantly decreased quantities of gametes besides female patients present with premature ovarian insufficiency(POI).It is well acknowledged that FA proteins take part in the DSB healing model of genetic recombination at the meiotic prophase; nevertheless,the actual association amongst their part in DNA healing as well as fertility has not been deeply detailed in humans[11].

DNA healing ability is variable amongst subjects along with association amongst decreased DNA healing ability along with proneness towards various kinds of haematological cancers has been acknowledged earlier. Akin to patients with BRCA1 mutations,where DOR was illustrated,girls as well as young women that in with impacted by leukaemia along with lymphoma(Hodgkin's as well as non Hodgkin's) further possessed decreased AMH quantities in the form of a marker of ovarian reserve before cytotoxic treatment was started as well[12].

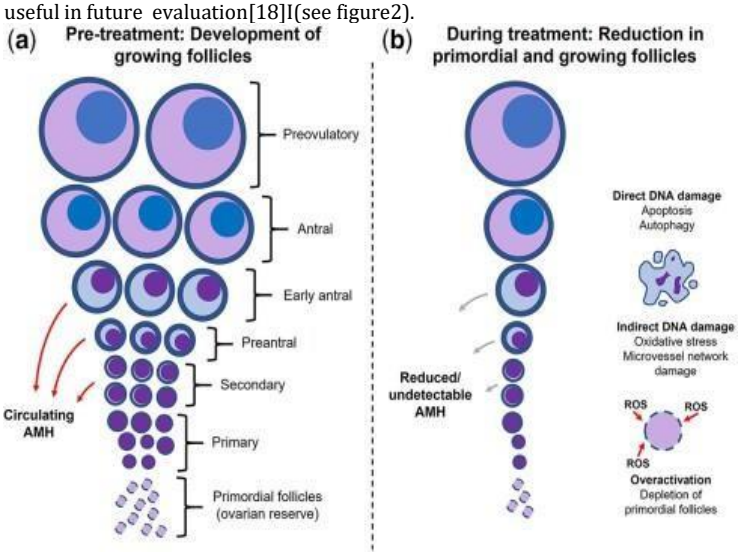
In theory these decreased AMH quantities could be attributed to dysfunctional granulosa cells working in view of dysfunctional DNA healing mode.Thus with background of observations of Oktay etal.[9], dysfunction of DNA healing ability might get shared for both,like besides escalating the chances of cancer generation, result in enhancement of premature ovarian aging along with DOR.Greater work regarding association amongst dysfunctional DNA healing system, cancer risk along with DOR is needed along with of great significance. Furthermore, in view of AMH quantities are frequent evaluation test in infertility, particular concentration needs to be done in young patients that possess lesser ovarian reserve naturally in view of their greater susceptibility of cancer generation risk once there is presence of dysfunctional DDR system. Moreover, young cancer patients apart from being susceptible to generation of DOR in view of cytotoxic therapy along with decreased quantities of gametes probably secondary to dysfunctional DNA healing ability. In view of them being prone to generation of considerable decrease of AMH quantities along with decreased recovery subsequent to chemotherapy fertility preservation strategies become imperative.

Once this posit gets corroborated in further studies, patients that possess lesser ovarian reserve naturally need to get cautioned about cancer screening for earlier aim of cancer avoidance that result in early intervening regarding long time health results[13].

Subsequently Verdiesen etal.[15],whose group had been earlier pursuing this research earlier[14], assessed longitudinal data from 3025 women in the prospective Doetinchem Cohort Study,using Cox proportional hazards models for evaluation of baseline age- AMH tertiles with cancer.. Their results did not give proof for a correlation amongst age-particular AMH and age-associated projections along with cancer risk. Nevertheless, effect estimates for breast cancer were in agreement with risk- escalating actions observed in prior studies.Their results were a little paradoxical in sense that they correlated greater AMH amounts in younger women in longitudinal studies in contrast to lower values in others but theirs was only longterm evaluation at different time periods while others had only checked single valuedespite them finding link with BC in these younger women[15].

Furthermore,role of diet was probed for the etiology of diet along with the risk of ovarian, endometrial, and breast cancer in menopause women[16]. There is evidence that diet is significant regarding various women's cancers, along with is correlated with cancer propagation,its survival, in addition to its therapy.They gave emphasis on Nutrigenetics, Nutrigenomics, as well as Nutritionalgenomics . The ideal combination regarding cancer avoidance was a diet having enrichment of Vitamins along with fibers as well as lesser meat ingestion,milkintake besides moderate utilization of alcohol.For that Mediterranean diet is apparently ideal having a greater nutritional paradigm making it ideal for prescription [17].

Recently in a a systematic review conducted by Anderson RA regarding Antimullerian hormone quantities in the form of a marker of ovarian reserve as well as premature ovarian insufficiency in children and women with cancer their observation wasthat in personalized subjects at variable ages inclusive of prepubertal adolescents girls in addition to contrasting with variable treatment regimens,ages as well as to pre treatment AMH quantities in population of women.They found proof regarding importance of POI following cancer therapy,future work over broad range of diagnosis along with treatment as well as ages of patients are required for clarity and quantification of anticipation value.The biggest short comings of utilization of AMH clinically was restricted results correlated with post therapy AMH quantities to fertility , time period of reproductive lifespan/time to POI generation; evaluation of these clinically significant results would prove to be useful in future evaluation[18]I(see figure2).



Courtesy ref no.18-Putative mechanisms of impact of cancer treatment on ovarian function. (a) In premenopausal individuals, circulating AMH is produced by secondary, preantral and early antral growing follicles, and has been shown in animal models to be one of several molecules which contribute to maintenance of ovarian reserve by inhibiting folliculogenesis; (b) anticancer treatment can reduce the ovarian pool of primordial follicles either by direct or indirect DNA damage, or by overactivation and subsequent depletion of primordial follicles; (c) following treatment, a patient may experience some recovery of the number of AMH-producing growing follicles, depending on the impact of anticancer treatment, or POI. In patients who recover ovarian function, a reduced pool of primordial follicles may still lead to an increased risk of later POI and infertility. AMH, anti-Müllerian hormone; POI, premature ovarian insufficiency; ROS, reactive oxygen species

Conclusions:

Having earlier reviewed the part of alkylating agents in particular implicated in decreasein PF pool along with methods of intervention[19-21],detailing modes implicated in decrease in PF,ORand POI here we further tried to see the recent posit by Oktay's groupregarding association of AMH low levels with women who are prone to generate cancer in view of correlation of DSB,DDR with normal meiotic events .Thus the dilemma persists if lesser AMH quantitiesin women with natural low AMH are predisposed to cancer forming and more probing is needed in view of correlation of DSB,DDR with normal meiotic events.

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