ISSN: 2755-6204

Case Study

Journal of Sexual Health and Reproductive Medicine

How Temporarily Reversing Menopause to Achieve 3 Children Led to A Novel Highly Effective Anti-Cancer Therapy- An Editorial

Jerome H. Check[1,2*] and Priya Srivastava[2]

[1]*Department of Obstetrics/Gynecology. Division of Reproductive Endocrinology and Infertility at Cooper Medical School of Rowan University Camden, NJ*

[2]*Cooper Institute for Reproductive Hormonal Disorders, Mt Laurel, NJ*

[*]**Corresponding author**

Jerome H Check, MD, Ph D, Cooper Medical School of Rowan University, Camden, NJ, USA.

Received: June 08, 2026; **Accepted:** June 12, 2026; **Published:** June 25, 2026

I recently wrote in conjunction with one of our medical students at Cooper Medical School of Rowan University named Naomi Ganpo Nkwenkwa, a series of 3 editorials and reviews on the role of membrane progesterone receptor associated proteins in gynecological and reproductive disorders and cancers [1-3]. For many years my main interest in medicine was cancer immunology, so I was heading down the path to become an oncologist, hematologist, and immunologist.

My basic science research goal was to make somewhat hidden onco-fetal antigens to become more exposed, and then use the killed tumor cells as a vaccine. We were having some initial success in murine cancers in mice with mammary adenocarcinoma and mice with lymphoma and leukemia [4-7].

However, I thought I had a better idea that could lead to an even more effective anticancer therapy in humans. It seemed logical that because of the similarity between a fetus and a malignant tumor, i.e., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, that the malignant tumor may hijack a mechanism(s) already in place to allow survival of the species.

Unfortunately, there was not much known at that time about how the fetal semi-allograft escaped immunosurveillance. Thus, I decided to temporarily switch fields, and instead of pursuing the intended oncology, hematology, and immunology fellowship, I proceeded with an OB-GYN/reproductive endocrine program and subsequently aimed to acquire a PhD in reproductive biology.

The details of the subsequent findings of our REI research leading to our treatment philosophy of today regarding treating infertility, preventing miscarriage, and preterm delivery and novel treatments for all types of pelvic pain and endometriosis has been elaborated in detail in the aforementioned three editorials [1-3].

However, to repeat, one of our key findings was the discovery of an immunomodulatory protein that we called the progesterone induced blocking factor (PIBF), that in the parent 90kDa form, encouraged rapid proliferation of embryonic, mesenchymal, trophoblast cells, and helped the fetal placental unit not tissue invade normal tissue. Furthermore, like progesterone and estrogen receptors, the parent 90kDa form of PIBF could be subdivided into splice variants. These splice variants also had immunosuppressive activity. Studies showed that this protein was able to neutralize the killing activity of the natural killer cells, macrophages, and cytotoxic T cells that invade the fetal placental microenvironment [8-10]. References 8 and 9 include the name of Dr. Szekeres-Bartho who with her team in Pecs Hungary performed many additional research studies that contributed to this hypothetical model I have detailed. Many of their studies can be found in references 1 and 2.

The PIBF protein was a product of P activating membrane P receptors (mPRs) to allow for the rapidity of suppression of the cellular immune cells in view of invasion into the endometrium of the fetal semi-allograft 6 days from fertilization. P activating nuclear PRs (nPRs) would constitute a genomic process which usually causes a much slower reaction time than the rapid action of mPRs. Possibly malignant tumors may secrete a small amount of P to activate the mPR but not enough to raise serum P levels. Alternatively, the malignant tumor may secrete other cytokines, enzymes, or proteins other than P to activate mPR.

Citation: Jerome H Check, Priya Srivastava. How Temporarily Reversing Menopause to Achieve 3 Children Led to A Novel Highly Effective Anti-Cancer Therapy- An Editorial. J Sex Health Reprod Med. 2026. 2(2): 1-9. DOI: doi.org/10.61440/JSHRM.2026.v2.46

The hope was that if I could prove that some or all cancers utilize PIBF to escape immune surveillance, then perhaps one could terminate cancer with a PR antagonist e.g., mifepristone, similar to its ability to terminate a live pregnancy. There was one thing that was disturbing. There was already evidence that there were some types of cancers, e.g., breast, ovarian, and endometrial that had the presence of nPRs. In view of the anti-cancer benefit of selective estrogen receptor modulators (SERMs) in treating nuclear estrogen receptor positive cancers, it was logical that one should try nPR antagonists. However, as I mentioned in the last editorial on mPRs, the results of treating cancer with a known nPR present with PR antagonists, e.g., mifepristone, was disappointing [3].

At that time, there was just the beginning of studies showing that patients positive for the nPR receptor may have a less aggressive cancer. Thus, possibly the mediocre response to mifepristone for nPR positive cancers could be related to suppressing a protective factor made by activating the nPR. The other possibility is the the presence of an nPR inhibits activation of the mPR.

Thus, the next logical step before proceeding with my intention of gavaging mice with a dosage of mifepristone that would be equivalent to the intended dosage for humans, i.e., 200 mg per day, and compare the length and quality of life in mice with a variety of spontaneous cancers would be to evaluate whether a cell line of a cancer that is negative for the nPR can not only secrete PIBF, but will show that mifepristone can suppress its secretion.

After my fellowship in reproductive endocrinology/infertility at Thomas Jefferson University, I stayed there in both the medical and OB-GYN departments. I stayed there in in both the medical and OB-GYN departments. I changed medical schools and hospitals not only to advance my rank to professor of obstetrics and gynecology and division head of reproductive endocrinology/infertility, but more important was my meeting with a hematologist/oncologist at the new medical school who was doing research with human leukemia cell lines and expressed initial willingness to collaborate with me to determine the next piece to the puzzle.

Unfortunately, after the hematologist canceled many planned meetings, I gave up on our collaboration.

Though initially, I thought I would pursue a fellowship in oncology hematology immunology, I developed a great interest in the field of reproductive endocrinology infertility (REI) not just in the research aspect, but in the clinical practice of REI.

Faced with many clinical challenges, I opened research studies aimed to improve certain pathological events leading to infertility or miscarriage outside of reproductive immunology. For example, what can we do about women with premature ovarian failure (POF) who want to conceive? Today most REI specialists think there is an easy solution, i.e., donor oocytes. However, even today when women are in apparent POF, when advised to "simply use donor oocytes," a very high percentage of patients are not satisfied with that option and seek opinions from other REIs to see if they are aware of any other therapeutic options.

Considering that a hormone must interact with a receptor to that hormone to exert its biological effect, and that there is generally a reciprocal relationship between a hormone and its receptor, (i.e., a high blood level of a hormone e.g., FSH, would likely down regulate FSH receptors to prevent receptor burnout). Whereas down regulation of steroid receptors is by shedding the receptors, down regulation of polypeptide hormones e.g., FSH and LH, involves internalization of the FSH receptor [11].

Thus, I hypothesized that in circumstances of very low serum estradiol (E2) and very elevated serum FSH, and long-term amenorrhea in women considered to be in overt menopause, possibly there are antral follicles still present that could become a dominant graafian follicle if the down regulated FSH receptors could be restored, i.e., up-regulated.

One way to lower serum FSH would be to treat with a gonadotropin releasing hormone (GNRH) agonist e.g., leuprolide acetate, whose long-term use would interfere with the pulsatility of GNRH and lead to reduction of the high serum FSH levels [12]. However, much less expensive, and with a better chance of inducing P receptors in the endometrium, and also stimulating cervical mucus, and allowing adequate thickness to the endometrium, would be to use the negative feedback effect of higher dosage estrogen on FSH release from the pituitary. The problem, however, would be that one would have to rely solely on follicular size by sonography to determine that a mature follicle was attained, but one would be unable to determine if the follicle was mature by serum E2 criteria. The ingestion of estradiol would raise the serum level.

I evaluated different types of estrogens to see which one would be able to suppress serum FSH yet contribute the least to the serum E2, so that we could determine if these women could make a mature follicle i.e., not only attaining an average diameter of 18 to 24 mm. but also a serum E2 200pg/ml or more. We concluded that the best estrogen to use was ethinyl estradiol (EE). Initially it existed on the pharmaceutical market; today it must be compounded by a pharmacy. Though ethinyl estradiol is present in most oral contraceptives, and could be used to suppress FSH release from the pituitary and induce follicular maturation, but the progestin would preclude implantation because of endometrial change.

Our first publication in 1984 showed that this technique enabled three of five women considered to be in overt menopause to ovulate and two became pregnant [13]. We subsequently published a few case reports in addition using this technique, which we call the "FSH receptor up regulation technique" [14-16]. By 1990 we reported the results of 100 women with POF treated with this technique which allows the recruitment of a follicle as evidenced by a rise in serum E2, with sometimes a boost with a small dosage of gonadotropins, and also progesterone support in the luteal phase [17]. In later years, the judicious use of GNRH antagonists e.g., ganirelix or cetrorelix was added once these drugs were manufactured.

With the advent of in vitro fertilization embryo transfer (IVF-ET) we showed that not only could menopause be reversed temporarily, but normal morphologic embryos can be created

that can lead to healthy babies [18-20]. For IVF, we modified the technique somewhat looking for a "sweet spot" where a small dosage of gonadotropins could be added to try to create more than one oocyte [21].

Some of these publications were prior to the consult by a physician who has granted permission to use her name, Maya Srivastava. She is the mother of my co-author Priya Srivastava. She was in premature ovarian failure due to bilatertal ovarian endometriosis, with management greatly complicated by Crohn's disease, but wanted her own genetic child. This was about 20 years ago.

However, despite consulting various REIs in Boston, Massachusetts, New Haven, Connecticut, and Cleveland, Ohio, they told her that ovulation induction in a menopausal woman was not possible. On her own, she had searched the literature and was aware of our previous publications. However, none of the REI's were willing to try this simple FSH receptor up regulation technique, still stating that inducing follicular maturation in a woman in overt menopause was impossible, and they doubted that the published cases from just one single REI group could have truly used patients that were definitely menopausal as was the state of depletion of Dr. Srivastava (even though one of these reports with successful ovulation and live delivery had bilateral streaked ovaries) [14].

Thus, she consulted the lead author in New Jersey. Dr. Srivastava not only had training in obstetrics and gynecology, but she had two years of REI researching nuclear progesterone receptors, isoforms, AP-1 and NFKB transcription factor/ mifepristone, interactions, but was also a board-certified pediatric gastroenterologist and an immunologist. In our very long first consultation, we shared our frustration, i.e., REIs closer to her geographic location, not believing in this technique to retrieve eggs from a woman in menopause, and my frustration over a stall in the cancer research because it did not seem that the aforementioned hematologist was ever going to collaborate with me and set up a study to determine if human leukemia cell lines could make PIBF , and hopefully show that mifepristone would suppress this PIBF activity.

Dr. Srivastava informed me that her father, Bejai Inder Sahai Srivastava PhD, had established and studied protein synthesis of various unique leukemia cell lines for over 30 years at Roswell Park Cancer Center in Buffalo, New York, including the effects of sex steroids on cytokine expression, and that we should collaborate on both problems; the reversal of her POF (and potential further scientific vindication of out technique helping others) and the further investigation of PIBF in cancer. She would modify and individualize the hormonal manipulations of our basic follicular sensitization technique with our guidance, carefully maintaining a scientific record, until succeeding or evident futility, and if a dominant follicle occurred, we would retrieve it, fertilize it, and freeze it. I refused to accept payment for these procedures. We all would work together in different labs across four states (NY, NJ, OH, PA) with her father Dr. Srivastava providing critical research support, and Maya herself, helping in the culturing and experimentation on the leukemia cell lines. Our results did show that a very large amount of messenger (m) RNA for PIBF was produced by many but not all different human leukemia cell lines of various lineages, as was the PIBF protein. Even better news was that the production of mRNA for PIBF and the protein itself was inhibited by the addition of mifepristone [22].

With this knowledge, it became worth the financial investment of using my own funds to evaluate the efficacy of using the weight equivalent of mifepristone that I would use in humans for very expensive mice bred for a high risk of certain spontaneous cancers [23-25]. With positive results from the murine spontaneous cancer studies and the human leukemia cell line data, the United States Food and Drug Administration (FDA) granted us permission to treat patients with very advanced cancers and without any other treatment options, and prescribe oral mifepristone 200 mg daily to these patients. FDA permission was required to use this drug off label, because the easy access to this drug was denied due to the sentiments of anti-abortionist groups. Thus, for each patient that we wanted to treat, we had to apply for and receive approval for a compassionate use investigator new drug (IND) application.

We have found that this drug can provide significant palliative benefits and extension of life in a variety of different cancers despite their very advanced, treatment resistant stage [26-29]. Single agent mifepristone therapy has allowed high-quality five-year survival in patients who had no more treatment options available [30,31].

One very aggressive form of non-small lung cancer (NSCLC) is a minority type that is positive for the epidermal growth factor receptor (EGFR) mutation. However, this is the type of NSCLC that may have the longest survival rate percentage with NSCLC because of their sensitivities to an anti-cancer type of drugs called tyrosine kinase inhibitors (TKI) [32]. Mifepristone therapy allowed two women to have good quality five years survival even after the cancer rapidly advanced with brain metastases despite treatment with the TKI inhibitor osimertinib [33].

One of the newer effective anti-cancer therapies is a class known as immune checkpoint inhibitors (ICIs). Merck pharmaceutical company advertises that their ICI pembrolizumab has been approved for 18 different types of cancers. Another ICI that appeared in the pharmaceutical market at the same time as pembrolizumab is a product made by Abbvie pharmaceuticals called nivolumab. Mifepristone has been found to be effective in advanced metastatic cancers that have progressed despite the patient having been treated with nivolumab [34]. Furthermore, mifepristone has allowed significant palliative benefits for some advanced cancers, e.g., pancreatic cancer and cholangiocarcinoma that are well known to be resistant to not only ICIs but to all types of chemotherapy [35-37].

Both ICIs and PR modulators (e.g., mifepristone) work to allow the immune system to now target these cancer cells that was being prevented by the production by the cancer cells of certain proteins that inhibit the immune system from recognizing them as foreign. One way that our normal cells inhibit cytotoxic T cells from attacking our own tissue is to provide a key (known as a

ligand) that is able to shut off the "motor" to the cytotoxic T cell. One of the shut off values for the motors is called program cell death factor-1 (PD-1). The ICIs are mostly directed against PD-1 or its ligand (PD-L1) using monoclonal antibodies to prevent the PD-L1 key from interacting with PD-1 and thus restarting the ignition to turn the motor back on to allow the cytotoxic T cell to once again police foreign invaders. When these monoclonal antibodies are used for suppression, it is called immunotherapy.

As mentioned, the use of a PR modulator/antagonist e.g., mifepristone uses a chemical drug to turn off the PR motor needed to make immunosuppressive proteins. PIBF is not needed in the non-pregnancy state, but is required for a mammalian fetus to escape immune surveillance until delivery. Thus, this type of treatment is not a form of immunotherapy, but a better term is immunoendocrine therapy [38]. One advantage of immunoendocrine therapy over immunotherapy with ICIs is that eventually the cancer cells find a way to turn off the killing action of the cytotoxic T cell by possible another pathway even if the program ccell death factor1 suppression valve is still operational.

In contrast, cancer cells do not seem to find an easy solution to remake the production of P IBF by the cancer cells with mifepristone as long as the mifepristone is continued (stopping it will usually lead to rapid death of the patient within three weeks). Though PIBF inhibits cytotoxic T cell attack of cancer cells, similar to ICIs, it also inhibits attack by natural killer cells [39].

One other major advantage of PR modulator type of immunoendocrine therapy versus immunotherapy with ICIs (not to mention the immense difference in price) is that ICI's enhance cytotoxic T cells activity against normal cells also. In contrast, PIBF is only needed during a pregnancy to allow the fetus to proliferate and escape immune surveillance, so there are no autoimmune side effects, and thus mifepristone is well tolerated. There was some concern that blocking the n PR in euestrogenic women could lead to endometrial hyperplasia or endometrial cancer. However, evaluating the efficacy of mifepristone treatment for benign meningiomas in a large series failed to find this complication [28]. It was not effective, however, because benign meningiomas do not produce PIBF [28].

This is only half of the story. The FSH receptor up-regulation technique allowed us to induce follicles leading to multiple eggs collected over many oocyte retrievals and fertilization of multiple embryos that were cryopreserved. The details of the cycle leading to the third child to be, a chromosomally normal male, was to be provided in a section called Case Report showing a success from an egg collection over 20 years ago from a woman in overt menopause was to be provided by my co-author Priya Srivastava, who is a pre-med student who was the first-born following embryo transfer from eggs fertilized after reversing menopause. Priya went overboard and summarized all of the IVF cycles with her mother, I decided it would lengthen this editorial too so we have submitted these details to J Sex Health and Reprod as a separate case report providing these details of all cycles with descriptions. Priya is the lead author in the submitted case report since she did the lion's share of data gathering and the writing of the case report. Her mother Maya was second author because Priya had to take an extensive history from her mother who also helped Priya in writing the case report, and myself last because I did the least amount of work in just slight modifications of the case report.

This submitted for publication case report will show that embryos created from eggs retrieved from a woman in overt menopause can not only withstand cryopreservation and survive thawing and most importantly lead to normal pregnancies that allowed a very intelligent physician to pass these intelligent genes to her very intelligent children. Aided by a gestational carrier, eggs obtained by reversing menopause allowed a woman to soon have 3 children 20 years apart and even have the third child with her own eggs at the age of 58.

Discussion

I was asked to write a review article by a different journal on diminished oocyte reserve (DOR) and POF. I agreed to do the review, but I wanted to make it more unique since I had written other reviews on the subject of DOR and POF using natural cycles or IVF-ET [42-44]. There are suggestions about other treatments to possibly help these women to attain a live delivery, including platelet rich plasma (PRP), stem cell injection, stimulation with human growth hormone, and the use of dehydroepiandrosterone (DHEA) supplementation, glucocorticoids, intravenous immunoglobulins, and intralipids. Thus, I decided that I would find the four latest review articles on DOR and POF and compare their opinions on these aforementioned auxiliary treatments, since we have never tried most of them ourselves because I was not impressed with any results that I saw from reviewing other published articles to warrant the extra expense.

The one exception was evaluating much less expensive DHEA supplementation, which not only did not provide impressive results in IVF-ET cycles, but seemed to show a trend for lower number of eggs retrieved and lower live delivered pregnancy rates (LDPRs) [45].

All four different sets of authors agreed that there was no clear-cut data suggesting efficacy of these auxiliary treatments. Though they mentioned the possible use of estrogen replacement, none of them described any resemblance of the FSH receptor up regulation technique [16,21]. None of the four mentioned the advantage of using ethinyl estradiol as opposed to estradiol [46]. Two of the four review articles had over 200 references and the other two had over 100 references and there was not one mention of any of our publications [47].

Thus, there is good evidence that the same lack of knowledge still exists concerning the induction of ovulation techniques in POI/POF patients and even apparent menopause, that existed 22 years ago when Dr. Srivastava, acting as her own advocate, located our prior publications on this technique and set her future family in motion. Though we have published from time to time over the years other cases of ovulation induction despite menopause in extremely unique cases, such as a 46 1/2-year-old woman in total menopause for about a year when she conceived on the very first cycle of ethinyl estradiol therapy to restore sensitivity to endogenous FSH. Her case was unique because she is the oldest woman to conceive with her own eggs despite menopause (the previous oldest was 45) [48]. This is

very important because we have never had a live delivery from a woman age 47 or higher using her own eggs no matter how good was her egg reserve. Secondly, it took her five cycles to get pregnant and have a successful delivery at age 42 when she had DOR with a serum FSH of 47mIU/ml. Her main prior infertility was related to the luteinized unruptured follicle syndrome, and she failed to release the egg in a natural cycle with the first evaluation without any treatment to help LUF, or two cycles of hCG, and the last with leuprolide acetate [49]. She was the first to show egg release despite LUF with the addition of a one-time injection of granulocyte-colony stimulating factor [50]. The third reason for publishing this case is that she suggests that in some very rare women the factors that lead to lower pregnancy rates with advancing age does not occur thus allowing a woman age 42 and 46 1/2 to conceive and deliver alive healthy full-term baby two out of two times when she released the eggs despite DOR the first time and POF the second time.

Another unique case was a 14-year-old girl with 45X Turner syndrome, primary amenorrhea, and sexual infantilism who was able to induce follicular maturation and freeze oocytes for the future both times that we used the same FSH receptor up-regulation technique [51].

My objective was to at least make the readers of Journal of Sexual Health and Reproductive Medicine familiar with this concept, so we recently described the technique for women with extremely low egg reserve or overt ovarian failure needing IVF-ET with successful pregnancies [52]. These cases had never been previously described.

I will still try to describe cases of ovulation in women with DOR or POF where there is a message to be given. We had previously published case reports of two women with DOR who were able to have three children over 8 years (one needing IVF-ET and one with natural pregnancies) [53,54]. So, we thought it also important to show that sometimes it takes longer to proceed to overt menopause, and sometimes much shorter, we recently published in J Sex Health Reprod Med a case report of a woman who successfully conceived with just progesterone alone when she had DOR but regular menses who subsequently went into overt ovarian failure during the pregnancy and thus needed to use ethinyl estradiol to restore sensitivity [55]. She successfully conceived again [55].

The actual recent review that included the views of four other authors on how to treat DOR and POF is entitled, "the relationship between diminished variant, reserve, and the increased cellular permeability syndrome" [47]. We have recently published articles, about the use of dopamine agonists such as dextroamphetamine sulfate to treat various aspects of pelvic pain related to increased cellular permeability in J Sex Health Reprod Med [56-58]. Recently, we published a case with a different type of pelvic pain i.e., severe vaginal burning, changing from severe dysmenorrhea which was ameliorated by cabergoline in a woman who had two babies, despite a diagnosis of POF [59].

We have been trying to emphasize the relationship of pelvic pain and DOR or POF related to excessive cellular permeability leading to excessive inflammation; but also emphasize it can be found with other clinical manifestations of the increased cellular permeability syndrome without pelvic pain e.g., inflammatory bowel disease, Crohn's disease or ulcerative colitis [60,61]. My co-author's mother, who was described in this editorial, had a history of both endometriosis and Crohn's disease.

Also, very importantly, a case recently described in J Sex Health Reprod Med makes a few new points. In this other case her mother had no clinical manifestations of the increased cellular permeability syndrome, except for having POF in her 30s. Yet her child not only manifested an extra pelvic malady i.e., severe mid-epigastric pain induced by eating, that was quickly abrogated by treating with dextroamphetamine. However, she had borderline egg reserve. The case illustrates the importance of checking egg reserve of children from women with DOR or POF because of the risk of autoimmune damage to the ovaries. The most unique aspects of this aforementioned recently published case are that early treatment with dextroamphetamine sulfate has allowed a significant improvement of her egg reserve to good levels as indicated by her serum AMH level which probably is related to more primordial follicles making it to the primary follicle stage [62].

There has been a case of twins that were born from embryos frozen 30 years ago. However, these were eggs from a woman with normal egg reserve. The brother on the way in this report is from an embryo frozen 20 years ago. We probably have others who have had three children despite POF but for sure, she will have the record for the most diversity of ages, i.e., siblings from a woman with POF with children ages 19, 8, and newborn (when he is born).

Final Thoughts

The main goal for writing this editorial is manyfold. As a scientist one hopes to contribute in some ways to helping mankind and to share discoveries with others. Though sharing of scientific information is far easier today because of computers, and internet, this leads to easy promulgation of the scientific information. Yet, apparently, most REIs and gynecologists are still unaware that ovulation and pregnancies can be achieved by techniques to restore sensitivity of follicles to FSH not merely a fortuitous rare spontaneous ovulation despite menopause. Also, part of my motivation is to acknowledge Bejai Srivistava Ph.D. who recently passed away. If not for his previous scientific studies of protein synthesis in human leukemia cell lines, that he established and kept culturing for over 50 years, we would not have had the opportunity to do the pivotal study to eventually find how PR antagonists can significantly improve the clinical status of so many patients suffering from cancer. Thus, it is hoped that this editorial/case report will promulgate the method to induce ovulation despite apparent menopause and help patients around the globe to share in this success. Just as important, to us is to share this new concept in cancer treatment to possibly extend the lives of patients with advanced cancer, and just as important, to stimulate the interest of other scientists to create an even more effective PR modulator to create a more superior anti-cancer drug [63].

Dr. Bejai Srivastava's willingness to collaborate in this cancer project enabled him to enjoy for a good number of years two

granddaughters. Furthermore, to pay it forward, his oldest granddaughter not only participated in writing this manuscript and a separate case report, which is important to her to make physicians more aware that there are relatively easy methods to even reverse menopause, let alone help people with DOR become pregnant. Our co-author is grateful to carry the genetics of her very intelligent grandfather and mother rather than be the product of a donor egg. Yet consults with most REIs and even experts in DOR are not aware of these simple inexpensive procedures. Donor egg procedures are extremely expensive. Interestingly, most cases of DOR or POF do not require IVF except for tubal factor (as in this case), or the need to cryopreserve embryos for the future (as in this case), or significant sperm abnormalities.

But speaking of "paying it forward," Dr. Maya and Priya Srivastava have been growing out the human leukemia cell lines once again, so we can collaborate in another study on the effect of mifepristone in suppressing other immunomodulatory proteins. Instead of PIBF, we want to evaluate another product of the mPR and that is the progesterone receptor modulator component-1 protein (PGRMC-1). We have speculated that interestingly in the dosages used for treating patients with cancer, a minimum of 200 mg a day and a maximum of 300 mg (the ceiling on the dosage is related to the fact that mifepristone dosage above that level will block the glucocorticoid receptors sufficiently to cause clinical adrenal insufficiency), the drug may act as an antagonist for PIBF but even be an agonist for PGRMC-1 [63]. If we find that a high percentage of human leukemia cell lines do produce PGRMC-1, as well as PIBF, but at the dosage comparable to be equivalent to the clinical dosage in humans, if at this dosage, there is up-regulation mRNA and the PGRMC-1 protein itself, (or at least no down regulation) then perhaps these results could influence some pharmaceutical companies to explore developing different PR modulators that also suppresses both PIBF and PGRMC-1 or do not block the glucocorticoid receptor thus allowing higher dosages to be given of the PR modulator to suppress both immunomodulatory proteins.

There are advantages and disadvantages of living in a country that has 100% socialized medicine or one that is 100% capitalistic. One hope of this editorial is to gain interest of a pharmaceutical company to become interested in the role of the mPR in cancer and put effort into research and development to develop a superior drug to mifepristone. Neither of these two authors have any patents for PR antagonists and are willingly gifting our research for the sole purpose of helping mankind. Because of the huge price of bringing a drug to market it is very understandable if a better PR antagonist is developed that it carries a high price which may be only available to wealthy patients or those patients who can afford the cost of very good health insurance. Mifepristone, in some countries taking one 200mg pill per day would cost less than 600 dollars per year. In the United States to pay without reimbursement would be about $15,000 per year. In contrast, the immune checkpoint inhibitors cost $500,000 to $1,000,000 per year.

Perhaps if insurance companies realized how much they would save by paying for mifepristone rather than other anti-cancer drugs, possibly they could be convinced to reimburse the cost of mifepristone. All the patients that we have treated with success had no side effects and had already been treated by ICIs or targeted therapies or standard anti-cancer therapy, and they failed to halt cancer progression. In contrast mifepristone did halt progression and provide not just extension of life but good quality of life [30,38]. There were some where mifepristone was the only anti-cancer drug used for treatment, but that is because the cancer was so advanced that the patient was advised that the best option was hospice [35].

Physicians have the right to use a drug off-label if there is evidence of its efficacy. One does not need to obtain a compassionate use IND any more for mifepristone, but the physicians must obtain it directly from the manufacturers since it has not been approved for distribution to pharmacies related to appeasing the sentiments of anti-abortion groups.

My co-author (PS) had another purpose of wanting to participate in writing this manuscript. She is on a mission to make young women aware that there are tests available to determine if their egg reserve is subnormal, and options available if so, e.g. oocyte freezing for the future or the use of dopamine agonists to slow the egg loss rate. I agree that one should not wait until some symptom develops e.g., oligomenorrhea or vasomotor symptoms. Serum AMH levels we believe should be obtained in their teenage years if their mother had DOR or POF and/or mother or child has a history of dysmenorrhea or other types of pelvic pain. Women on oral contraceptives where symptoms of DOR would be masked could consider having a serum AMH level obtained every 1-2 years.

We also hope that by writing this editorial, we make the medical community more aware that women with pelvic pain or other manifestations of the increased cellular permeability syndrome are more prone to miscarriage. As a minimum they should be using supplemental P in the luteal phase, and probably daily use of a dopamine agonist, e.g., dextroamphetamine sulfate to maximally suppress the possibility of excessive inflammation with fetal immune rejection.

This would have applied to my co-authors mother if she was to deliver the baby herself, in view of her history of dysmenorrhea, endometriosis, and Crohn's disease and POF. However, that was not needed in her case since a gestational carrier was used for all three pregnancies.

Finally, one of the purposes of writing this editorial is to make the medical community more aware of the alternative of using dopamine agonists for multiple inflammatory/autoimmune medical conditions rather than potent immunosuppressive agents with their risk of serious side effects e.g., infection, or later development of cancer, not to mention their great expense. Despite publishing over 100 case reports and summaries of the various types of pathological disorders that were refractory to standard therapy, but responded so well to dopamine agonists e.g., dextroamphetamine sulfate, not only has this concept not become credible to the medical community, but governmental agencies seem to be on a mission to stop the use of the dopamine agonist that has provided the most experience and success, i.e., dextroamphetamine sulfate. Nevertheless, we hope that we can stimulate interest in other clinicians to evaluate other dopamine

agonists for treating many chronic treatment resistant disorders whose etiology may be on an autoimmune basis e.g., cabergoline and carbidopa-levodopa and publish their outcomes whether positive or negative [64].

References

1. Check JH, Ganpo NN. The role of membrane progesterone receptor associated proteins in gynecological and reproductive disorders, and cancers: an editor's historical perspective, Part 1: Molecular Aspects Submitted to Journal of Sexual Health and Reproduction J Sex Health Reprod Med. 2026. 2: 1-6.
2. Check JH, Gampo NN. The role of membrane progesterone receptor associated proteins in gynecological and reproductive disorders, and cancers: an editor's historical perspective: Part 2: Clinical benefits of P supplementation post-ovulation. J Sex Health Reprod Med. 2026. 2: 1-8.
3. Check JH, Nkwenkwa-Ganpo N. The role of membrane progesterone receptor associated proteins in gynecological and reproductive disorders, and cancers: an editor's historical perspective Part 3: The role of mPRs and immunomodulatory proteins in development of benign and malignant tumors and endometriosis. J Sex Health Reprod Med. 2026. 2: 1-10.
4. Check JH, Childs TC, Brady LW, Derasse AR, Fuscaldo KE. Protection against spontaneous mouse mammary adenocarcinoma by inoculation of heat treated syngeneic mammary tumor cells. Int J Cancer. 1971. 7: 403-408.
5. Check JH, Brady LW, Leipold PL, O'Neill EA. Protection against transplanted and spontaneous lymphoma by inoculation of heat-altered syngeneic tumor cells in splenectomized mice. Cancer. 1974. 34: 197-203.
6. Check JH, Brady LW, O'Neill EA. Differences in the protective effect of complete Freund's adjuvant in spontaneous versus transplanted lymphomas in AKR mice. Immunology of Cancer. Prog Exp Tumor Res. 1974. 19: 217-221.
7. Check JH, Silverman GA, Dryden RL, Brady LW. Inhibition of spontaneous AKR Leukemia by multiple inoculations of corynebacterium parvum. Cancer. 1979. 44: 488-491.
8. Check JH, Szekeres-Bartho J, O'Shaughnessy A. Progesterone induced blocking factor seen in pregnancy lymphocytes soon after implantation. Am J Reprod Immunol. 1996. 35: 277-280.
9. Check JH, Arwitz M, Gross J, Szekeres-Bartho J, Wu CH. Evidence that the expression of progesterone-induced blocking factor by maternal T-lymphocytes is positively correlated with conception. Am J Reprod Immunol. 1997. 38: 6-8.
10. Check JH, Aly J. Improving the chance of successful implantation – part 2 – Circumventing immune rejection and the fetal semi-allograft. Clin Exp Obstet Gynecol. 2018. 45: 9-13.
11. Check JH. Understanding the physiology of folliculogenesis serves as the foundation for perfecting diagnosis and treatment of ovulatory defects. Clin Exp Obstet Gynecol 2012. 39: 273279.
12. Check JH, Wu CH, Check M. The effect of leuprolide acetate in aiding induction of ovulation in hypergonadotropic hypogonadism: A case report. Fertil Steril. 1988. 49: 542-543.
13. Check JH, Chase J. Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy. Fertil Steril. 1984. 42: 919-922.
14. Check JH, Chase JS, Wu CH, Adelson HG. Case Report. Ovulation induction and pregnancy with an estrogen-gonadotropin stimulation technique in a menopausal woman with marked hypoplastic ovaries. Am J Ob-Gyn. 1989. 160: 405-406.
15. Check JH, Nowroozi K, Nazari A. Viable pregnancy in a woman with premature ovarian failure treated with gonadotropin suppression and human menopausal gonadotropin stimulation: A case report. J Reprod Med. 1991. 36: 195-197.
16. Check JH, Choe JK. Maximizing correction of infertility with moderate to marked diminished egg reserve in natural cycles by up-regulating follicle stimulating hormone receptors. Gynecol Reprod Health. 2022. 6: 1-7.
17. Check JH, Nowroozi K, Chase JS, Nazari A, Shapse D, Vaze M. Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea. Fertil Steril. 1990. 53: 811-816.
18. Check JH, Nowroozi K, Nazari A, Baker A, Goldsmith A. In vitro fertilization-embryo transfer in three women with ovarian failure. J IVF-ET. 1990. 7: 45-46.
19. Check JH, Summers D, Nazari A, Choe J. Successful pregnancy following in vitro fertilization-embryo transfer despite imminent ovarian failure. Clin Exp Obstet Gynecol. 2000. 27: 97-99.
20. Check ML, Check JH, Choe JK, Berger GS. Successful pregnancy in a 42-year-old woman with imminent ovarian failure following ovulation induction with ethinyl estradiol without gonadotropins and in vitro fertilization. Clin Exp Obstet Gynecol. 2002. 29: 11-14.
21. Check JH. A follicle stimulating hormone (FSH) receptor up-regulation technique as a method for follicular recruitment for in vitro fertilization-embryo transfer in women with diminished oocyte review. Ed. Leon V. Berhardt; In: Advances in Medicine and Biology, Nova Science Publishers, Inc., Hauppauge, NY, 2022. 195: 119-137.
22. Srivastava MD, Thomas A, Srivastava BI, Check JH. Expression and modulation of progesterone induced blocking factor (PIBF) and innate immune factors in human leukemia cell lines by progesterone and mifepristone. Leuk Lymphoma. 2007. 48: 1610-1617.
23. Check JH, Sansoucie L, Chern J, Amadi N, Katz Y. Mifepristone treatment improves length and quality of survival of mice with spontaneous leukemia. Anticancer Res. 2009. 29: 29772980.
24. Check JH, Sansoucie L, Chern J, Dix E. Mifepristone treatment improves length and quality of survival of mice with spontaneous lung cancer. Anticancer Res. 2010. 30: 119-122.
25. Check JH, Dix E, Wilson C, Check D. Progesterone receptor antagonist therapy has therapeutic potential even in cancer restricted to males as evidenced from murine testicular and prostate cancer studies. Anticancer Res. 2010. 30: 4921-4924.
26. Check JH, Dix E, Sansoucie L, Check D. Mifepristone

may halt progression of extensively metastatic human adenocarcinoma of the colon – case report. Anticancer Res. 2009. 29: 16111613.

27. Check JH, Dix E, Cohen R, Check D, Wilson C. Efficacy of the progesterone receptor antagonist mifepristone for palliative therapy of patients with a variety of advanced cancer types. Anticancer Res. 2010. 30: 623-628.
28. Check JH, Check D. Therapy aimed to suppress the production of the immunosuppressive protein progesterone induced blocking factor (PIBF) may provide palliation and/or increased longevity for patients with a variety of different advanced cancers – A review. Anticancer Res. 2019. 39: 3365-3372.
29. Check JH, Check D. Mifepristone may be the best single pharmaceutical agent for treatment of a variety of advanced cancers. Cancer Sci Res. 2021. 4: 1-6.
30. Check JH, Check DL, Wilson C. Good quality (66.7%) 5-year overall survival in terminal lung cancer patients treated with mifepristone. Anticancer Res. 2025. 45: 5785-5798.
31. Check JH, Check D, Poretta T, Wilson C. Palliative benefits of oral mifepristone for the treatment of metastatic fibroblastic osteosarcoma. Anticancer Res. 2021. 41: 2111-2115.
32. Check JH, Poretta T, Check D, Srivastava M. Lung Cancer - Standard therapy and the use of a novel, highly effective, well tolerated, treatment with progesterone receptor modulators. Anticancer Res. 2023. 43: 951-965.
33. DL, Check JH, Poretta T, Aikins J, Wilson C. Prolonged high-quality life in patients with non-small cell lung cancer treated with mifepristone who advanced despite osimertinib. Cancer Sci Res. 2020. 3: 1-5.
34. Check JH, Check D, Poretta T. Mifepristone extends both length and quality of life in a patient with advanced non-small cell lung cancer that has progressed despite chemotherapy and a check-point inhibitor. Anticancer Res. 2019. 39: 1923-1926.
35. Check JH, Check D, Srivastava MD, Poretta T, Aikins JK. Treatment with mifepristone allows a patient with end-stage pancreatic cancer in hospice on a morphine drip to restore a decent quality of life. Anticancer Res. 2020. 40: 6997-7001.
36. Check JH, DiAntonio A. Though pancreatic cancer may be resistant to immunotherapy from immune check-point inhibitors, it may be sensitive to blocking production of immunoprotective proteins unique to pregnancy. IgMin Res. 2026. 4: 110-115.
37. Check JH. Evidence that the use of progesterone receptor modulators/antagonists can provide palliative benefits for a moribund patient with cholangiocarcinoma. Int J Med Pharm Res. 2025. 6: 162-164.
38. Check JH. Novel immunoendocrine therapy of advanced cancers of all types opens a new medical field for clinical and research endocrinologists. Am J Biomed Sci Res. 2024. 23: 86-98.
39. Check JH, SanSoucie L, Chern J, Amadi N, Srivastava M, et al. Evidence that progesterone receptor antagonists may help in the treatment of a variety of cancers by locally suppressing natural killer cell activity. Clin Exp Obst Gynecol. 2007. 34: 207-211.
40. Check JH, Srivastava M, Brasile D, Amui J, Choe JK, et al. Successful pregnancy with frozen embryo transfer into a gestational carrier from eggs obtained from a woman in premature menopause – case report. Clin Exp Obstet Gynecol. 2009. 36: 154-157.
41. Check JH, Cohen R. A second successful pregnancy using oocytes from a woman with premature ovarian failure with embryos transferred to a gestational carrier. Clin Exp Obstet Gynecol. 2017. 44: 507-508.
42. Neumann B, Check JH, Sobel M, Hollahan K, Wilson C. A study to determine the impact of diminished oocyte reserve (DOR) on pregnancy outcome in women of advanced reproductive age. Gyn Reprod Health. 2024. 8: 1-3.
43. Check JH, Neumann B, Check DL, Sobel M. A study to determine the reason for lower pregnancy rates in younger woman with diminished oocyte reserve –less chance of implementing vs feral demise. IgMin Res. 2024. 2: 364-366.
44. Check JH, Neumann B, Sobel M, Wilson C, Summers D. IVF outcome: Advanced female age, low egg reserve, Int J Obst Gyn. 2025. 5: 1-3.
45. Borman E, Check JH, Mitchell-Williams J, Cohen R. No evidence to support the concept that low serum dehydroepiandrosterone (DHEA) sulfate (s) levels are associated with less oocyte production or loer pregnancy rates. Clin Exp Obstet Gynecol. 2012. 39: 429-431.
46. Check JH. The multiple uses of ethinyl estradiol for treating infertility. Clin Exp Obstet Gynecol. 2010. 37: 249-251.
47. Check JH, Neulander M, Check DL, O'Neil MM, Wilson CBS. The relationship between diminished ovarian reserve and the increased cellular permeability syndrome. Int J Clin Med Case Stud. 2025. 2: 1017.
48. Check JH, Check DL, Richardson K. Live delivery in a 46.5-year-old woman in overt menopause by restoring follicular sensitivity to follicle stimulation (FSH). Gynecol Reprod Health. 2022. 6: 1-3.
49. Check JH, Nazari A, Barnea ER, Weiss W, Vetter BH. The efficacy of short-term gonadotrophin-releasing hormone agonists versus human chorionic gonadotrophin to enable oocyte release in gonadotrophin stimulated cycles. Hum Reprod. 1993. 8: 568-571.
50. Check JH, Vaniver J, Senft D, DiAntonio G, Summers D. The use of granulocyte colony stimulating factor to enhance oocyte release in women with the luteinized unruptured follicle syndrome. Clin Exp Obst Gynecol. 2016. 43: 178-180.
51. Check JH, Neumann BA, Horwath D, Summers D. Oocyte freezing following ovulation induction and egg retrieval in a 45X teenage girl with hypergonadotropic primary amenorrhea, estrogen deficiency, and sexual infantilism. Gynecol Reprod Health. 2024. 8: 1-3.
52. Check JH, Covolesky S, DiAntonio A. A Detailed Description of the FSH Receptor up Regulation Technique Employed to Develop Metaphase II Oocytes for in Vitro Fertilization Embryo Transfer in Women with Extremely Low Egg Reserve who had Successful Pregnancies. J Sex Health Reprod Med. 2026. 2: 1-7.
53. Check JH, Katsoff B. Three successful pregnancies with in vitro fertilization embryo transfer over an eight-year time span despite elevated basal serum follicle stimulating hormone levels – Case report. Clin Exp Obstet Gynecol. 2005. 32: 217-221.

54. Check JH, Giangreco J. Three successful pregnancies following natural conception over an 8-year time span despite serum follicle stimulating hormone level greater than 15 mIU/mL – case report. Clin Exp Obstet Gynecol. 2009. 36: 12-14.
55. Check JH, Srivastava P. Two successful pregnancies in a woman with marked diminished ovarian reserve-one with regular menses and one in overt menopause. J Sex Health Reprod Med. 2026. 2: 1-3.
56. Check JH. Increased Cellular Permeability Related to Relative Dopamine Deficiency May Play a Major Role in the Etiology of Dyspareunia by Causing Inflammation. J Sex Health Reprod Med. 2025. 1: 1-7.
57. Check JH, Carpenteier P, Meier B, Ganpo-Nkewnkwa N. Dopaminergic drug very effective for relieving pelvic pain in women even when hormonal therapy and surgery were not sufficient. J Sex Health Reprod Med. 2025. 1: 1-4.
58. Check JH, Ganpo Nkwenkwa N. Marked relief of painful ejaculation (Dysogasmia) in a young male treated with the dopaminergic drug dextroamphetamine sulfate. J Sex Health Reprod Med. 2025. 1: 1-3.
59. Check JH, DiAntonio A. Dopamine agonists aiding in successful follicular development and two live deliveries despite premature ovarian failure and ameliorating severe vaginal pain. Int Gyn & Women's Health. 2026. 6.
60. Check JH, Check DL, Neumann B. A Novel Treatment of Crohn's Disease that is Not Only Safe in Pregnancy but Can Correct Infertility and Recurrent Miscarriages. Gynecol Reprod Health. 2024. 8: 1-9.
61. Check JH, Neumann B. Combined Dopaminergic Drugs with Supplemental Progesterone to Treat Recurrent Miscarriage and Ulcerative Colitis despite Diminished Egg Reserve. Gynecol Reprod Health. 2024. 8: 1-10.
62. Check JH, Ganpo-Nkwenkea, Srivastava P. Besides abrogating an unusual case of eating induced mid-epigastric pain, treatment with dextroamphetamine may help to increase oocyte reserve in a young teenage girl possibly heading from premature menopause. J Sex Health Reprod Med. 2025. 1: 1-5.
63. Check JH, Check D, Neumann B. Future directions to explore to develop ideal anti-cancer progesterone receptor modulators. Cancer Sci Res. 2023. 6: 1-8.
64. Check JH, Srivastava P, Kelley C. The relative efficacy of three different dopamine agonists in relieving symptoms of various manifestations of the increased cellular permeability syndrome. Case report. Int J Clin Med Case Stud. 2025. 2: 1039.