Incorporating New Hormonal Technology to Help Couples Avoid Pregnancy During and After Chemotherapy

*Richard J. Fehring, PhD, RN, FAAN**
*Thomas Bouchard, MD***

Abstract: Women who have cancer are often warned by their physician not to get pregnant. A pregnancy can result in making decisions about the life of the mother and the unborn baby. Sterilization (both male and female) is a common method used for reproductive age women who are being treated for cancer. However, for many women and couples the use of sterilization or other methods of contraception would not be a moral choice. These women and couples often are seeking secure natural means to avoid pregnancy. New quantitative hormonal monitoring systems now provide women with the ability to monitor their reproductive hormones for securely avoiding pregnancy and for diagnostic purposes. This paper will describe this new reproductive hormonal technology and its use in case studies of women who are being treated for cancer.

∗Richard J. Fehring, PhD, RN, FAAN, is Professor Emeritus and past Director of the Marquette University College of Nursing Institute for Natural Family Planning. He received his master's degree and doctorate in nursing from Catholic University of America and baccalaureate degrees in biology and nursing from Marquette University. He has published over 200 articles and book chapters, coedited three books and has generated over $3 million in research and foundation grants. His research interests include effectiveness of fertility awareness methods of family planning, marital responses to family planning, and religious influences on human sexuality.

**After completing his undergraduate at McGill University, Dr. Thomas Bouchard completed medical school and residency at the University of Calgary. He now practices general family medicine at Westglen Medical Centre and geriatric care at two nursing homes. His special interests include primary care approaches to fertility, menstrual health literacy and perinatal palliative care. Alongside his clinical practice he has started a part-time PhD at the University of British Columbia focused on menstrual cycle monitoring.

WOMEN OF REPRODUCTIVE AGE WHO HAVE CANCER are often warned by their physician not to get pregnant, or that chemotherapy for cancer may have unknown impacts on fertility. A pregnancy can result in making decisions about the life of the mother and the unborn baby. Pregnancy might reduce her chance for optimum treatment of the cancer, make the cancer more aggressive, or the cancer treatments might result in damage to the growing fetus. Since hormonal contraceptives would also not be an option for contraception as the synthetic hormones (in oral contraceptive pills, implants or IUDs) could stimulate the cancer and barrier methods are not adequately effective, non-hormonal IUDs and sterilization have been recommended.[1]

Many couples have moral and religious reasons for not using contraception or sterilization and for those wanting future pregnancies and children, sterilization would not be an option. Other alternatives would be to remain abstinent from sexual intercourse during treatment or indefinitely. or they could choose to use a natural method of family planning (i.e., natural family planning or NFP). However, the use of NFP would need to be truly effective in helping women and their spouses for avoiding pregnancy given the serious reasons to avoid harm to the unborn baby from the potential cancer treatments. There are some very effective NFP methods but there is very little published research in the use of NFP among women being treated

[1] Mayo Clinic Web Site "Fertility, birth control and pregnancy in breast cancer survivors: Answers to common questions" https://mcpress.mayoclinic.org/cancer/fertility-birth-control-and-pregnancy-in-breast-cancer-survivors-answers-to-common-questions/ Retrieved June 22, 20124.

for cancer. Thankfully, there is now available technology that can enable the woman with cancer and her spouse to track the fertile time of the menstrual cycle with new quantitative hormonal self-monitoring devices. [2]

The purpose of this paper is to describe the new female hormonal monitoring systems and to present two cases of women with cancer who are using hormonal monitoring technology to avoid pregnancy. The paper ends with a discussion of the implications for using hormonal monitoring technology in difficult cases.

New Hormonal Monitoring Technology

In a previous paper, three case scenarios were presented of women (and their spouses) who were experiencing difficult life situations in which if they had an unintended pregnancy; the pregnancy could be detrimental to the woman or her unborn baby. The current medical profession would recommend an abortion and/or recommend sterilization for either the woman or her spouse to prevent an unintended pregnancy.[3] The three cases involved: 1) a woman with breast cancer and on a medication that may increase risk to harm a child in utero; 2) a woman with five children and is currently breastfeeding an infant, and 3) a perimenopausal woman who has a health problem and a greater risk for a child with Down Syndrome.

The use of a modern NFP method and special protocols developed by researchers at Marquette University to manage these special problems was presented with use of an electronic hormonal fertility monitor, the ClearBlue Fertility Monitor (CBFM). This monitor enabled women users to monitor their fertile phase with measuring a metabolite of estrogen and luteinizing

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[2] Thomas P. Bouchard, Richard J. Fehring & Qiyan Mu (2021): Quantitative versus qualitative estrogen and luteinizing hormone testing for personal fertility monitoring, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2021.2000393; Qiyan Mu and Richard Jerome Fehring (2023). A Comparison of Two Hormonal Fertility Monitoring Systems for Ovulation Detection: A Pilot Study. Medicina 2023, 59(2), 400; https://doi.org/10.3390/medicina59020400 - 18 Feb 2023

[3] Fehring, R., (2017). Preventing unintended pregnancies (the natural way) among women with hard cases. *Life and Learning* XXIII. In Proceedings of the Twenty Third (2013) Conference of University Faculty for Life. (Ed. J. Koterski). P 255-270.

hormone (LH) to qualitatively estimate the fertile phase of their menstrual cycle in their urine. The CBFM provided three levels of fertility (Low, High, and Peak). The High reading began when a ripe egg within a follicle was developing and secreting estrogen—which indicated the beginning of the fertile window. A surge in LH provides a Peak reading and pending ovulation within 24-26 hours. After ovulation the egg released from the developing follicle lives for only 12–24 hours and ends the fertile phase.

Although this monitor provides the women and couple with an objective estimate of the biological fertile window, it does have some limitations. First, it only provides a qualitative level of reproductive hormones. It would be nice to have the actual levels to be able to make a more informed decision about the menstrual cycle and the fertile phase. Another limitation is that there is no confirmation that ovulation took place after the LH surge. An LH surge can happen without ovulation with women who have various health problems like polycystic ovarian syndrome. The ability to measure the hormone progesterone would help with this limitation in that progesterone rises after ovulation and provides a confirmation that ovulation has taken place and that the woman in now in her post-ovulatory infertile phase.

In the last several years several hormonal monitoring systems have been developed that address these limitations. The new hormonal monitoring systems now not only provide quantitative levels of the reproductive hormones but also include progesterone, which can help determine if ovulation has taken place. Another advancement is that these devices are for home use and are connected to an interactive smartphone App to provide graphic displays of the hormones and the menstrual cycle. Furthermore, the graphic displays and health information are also linked to an online dashboard for their health provider. The provider sees in real time the hormone levels and a graphical picture of the menstrual cycle.

Researchers and clinicians at Marquette University institute for Natural Family Planning have been investigating the use of the Mira hormonal monitor (Mira) and have developed tentative protocols for estimating the fertile window. They are also investigating the use of Mira in special cases such as during the postpartum transition to fertility, during perimenopause,

and during the treatment of cancer.[4,5] The following two case studies illustrate the use of Mira among two women being treated for cancer.

Case Study One

The first case involves a 47-year-old female diagnosed with breast cancer. The client completed 12 rounds of chemotherapy and then started tamoxifen on 7/1/2022. She started testing with Mira in mid-June. She had bilateral mastectomy surgery on 9/15/2022. She stopped the tamoxifen therapy 2 weeks before her surgery and resumed it approximately 2 weeks after surgery. She has not had a menstrual bleed since starting chemotherapy.

She reports that her recovery time from the surgery was long, since she had chemo first and did not have reconstructive surgery. Part of her recovery included 8 weeks of compression wrapping. Overall, the surgery went well as the "margins were good" and 13 lymph nodes were removed. She began radiation therapy on 11/08/2022. She resumed her tamoxifen on 10/30/2022 after not taking it from 08/31/2022–10/30/2022. Prior to her surgery, she took tamoxifen from 07/01/2022–08/31/2022. Her oncologist wanted her to take tamoxifen for 6 months and then move to a different hormone blocker. She had blood work on 10/13/2022 and her LH was 67.6 mlU/ml, her follicle stimulating hormone (FSH) was 94.6 mlU/ml, and her Estradiol 21.4 pg/mL. Based on her high levels of FSH and LH and low levels of estrogen, her oncologist stated that she was most likely in menopause. Figure 1 shows her LH, E3G, and PDG levels.

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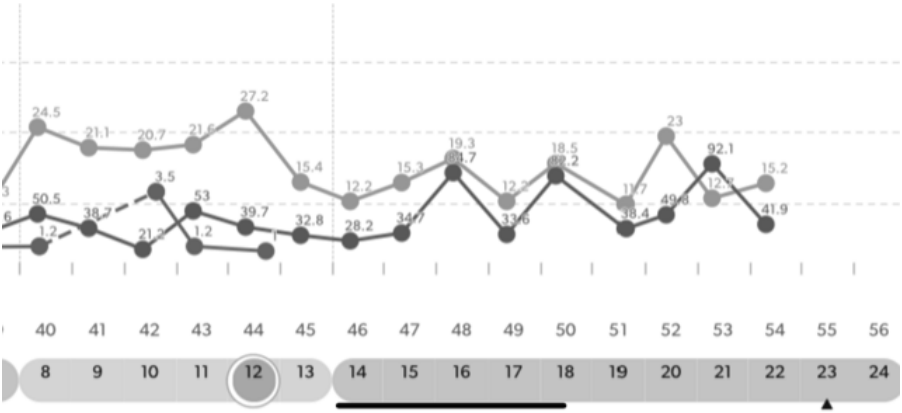
[4] Mary M. Schneider, Richard J. Fehring, and Thomas Paul Bouchard. (2023). Effectiveness of a Postpartum Breastfeeding Protocol for Avoiding Pregnancy. *The Linacre Quarterly*, https://orcid.org/0000-0001-9071-4813, OnlineFirst, 90(2): 182-193.

[5] Maria Meyers, Richard Jerome Fehring, and Mary Schneider (2023). Case Reports from Women Using a Quantitative Hormone Monitor to Track the Perimenopause Transition. *Medicina* 2023, 59(10), 1743; https://doi.org/10.3390/medicina59101743.

Figure 1: Mira results with LH in light Blue, estrogen in Black, and Progesterone in Purple—showing high levels of LH and low levels of estrogen and progesterone and thus an infertile state.



At 47 her fertility is less than 1–2 % without calculating her being on chemo and tamoxifen. With high blood levels of LH and FSH, her oncologist's assessment may fit with entering menopause, i.e., 12 months without an ovulation and menses, but it may also reflect temporary anovulation and amenorrhea. However, at times she has elevated levels of E3G, which may be a result of tamoxifen, which may stimulate the follicular development with normal appearing estrogen levels, despite her low level of fertility based on age and aging ova. Overall, the likelihood of pregnancy is very low.

Being on tamoxifen also causes hot flushes (85%), disturbed sleep (55%), vaginal dryness and/or dyspareunia (47%) and lower libido. Tamoxifen can have an estrogenic effect and increase estrogen levels, blocking estrogen from attaching to cancer cells. Note that postmenopausal women will also have an estrogenic effect from tamoxifen-estrogen, not from any follicles. If she is not having any menstrual bleeding, I suspect —as the oncologist does —that she is in a menopausal state.

Comment from two physicians:

Thomas Bouchard, MD, Family Medicine Physician

With sustained high LH she is infertile regardless of the E3G fluctuations. I would suggest she look for lowering LH to levels below 11, in a sustained way, and then rise in E3G and then rise in LH in a surge-like fashion if she were to ovulate. Based on these numbers I would say she is infertile.

Specific "protocols" for difficult cases such as this are not always easy to recommend because of the lack of research for protocols. In the following study and others, as Dr. Fehring mentioned, Tamoxifen can induce high levels of estrogen, but this does not mean that folliculogenesis is occurring.

Maria Meyers, MD, Pediatrician

Bottom line, her high E3G levels could be induced by tamoxifen, but her lack of cycles in 12 months really points to menopause, no probable need for tracking. Neither her E3G levels nor LH levels may be indicative of what is happening at the ovarian level, which is probably ovarian failure. Maybe an AMH level would indicate her low ovarian reserve and give her peace of mind.

Due to her recently elevated LH levels, the "rule" we developed while taking tamoxifen is: If estrogen is below 100 and LH ABOVE 11 yesterday and today, then today is usable. We are planning to meet again after her surgery and after resuming tamoxifen.

Case Study Two

The second case involves a 38-year-old woman with a new diagnosis of stage II breast cancer. She was prescribed several chemotherapy medications (Taxotere, Carboplatin, Trastuzumab, and Pertuzumab). After her rounds of chemotherapy were completed, she was placed on Herceptin which is used to treat Her2 gene positive breast cancer. This medication has a 50% chance of chemo-induced menopause.

She proceeded to have one normal menstrual cycle after starting chemotherapy. After her third round of chemo, she began recording multiple LH surges with multiple “Peak” readings on the Clearblue monitor and positive LH tests without evidence of ovulation (no thermal shift, low serum progesterone). Due to client frustration with unclear fertility patterns and continued abstinence to avoid pregnancy, we began using Mira to evaluate her patterns of E3G and LH.

It was proposed to use the Mira monitor to determine infertility using an estrogen threshold of 150 ng/mL, or more conservatively, 100 ng/mL. The client opted to use 100 ng/mL as the threshold, asking herself two questions to determine if the day would be infertile: 1) Is my estrogen below 100 today? and 2) Was my estrogen below 100 yesterday? If yes to both questions, the day was considered infertile. It was made clear to the client that this proposed set of instructions has not been researched for effectiveness of avoiding pregnancy, and no information is available for use of the Mira monitor in women undergoing cancer treatment.

One incident of what appeared to be an anovulatory bleed lasting 13 days occurred at the start of testing with the Mira monitor. After the bleed, the client's E3G readings remained below 150 ng/mL for several weeks, while LH levels remained elevated (See Figure 2).

The client's last dose of chemotherapy was on August 27th, and the client underwent a bilateral mastectomy on October 7th. In November, approximately two months after discontinuation of chemotherapy, the Mira E3G results consistently remained elevated above 200 ng/mL, signaling a potential return of ovarian activity (See Figure 3). LH levels also showed a changing pattern, gradually lowering over several weeks. The estrogen levels remained elevated for 40 days until eventually an LH level of 124 mIU/mL was recorded alongside an E3G level of >640 ng/mL (the highest level the Mira monitor will display). Five days later, a urine PDG test showed a positive result, indicating a probable ovulation. The client started her menses after a 12-day luteal phase and returned to a regular fertility pattern in subsequent cycles (See Figure 4).

Upon consultation, the client reported frustration with extended abstinence during times of unclear fertility status, such as prolonged elevated E3G and LH as indicated on the Mira monitor, and multiple anovulatory "Peak" readings from the Clearblue monitor. However, the client did state satisfaction using the recommendation of E3G remaining below 100 ng/mL the day of and the day before to determine non-fertile days while experiencing anovulation from chemotherapy. The client reported she and her spouse were comfortable resuming intercourse while avoiding pregnancy when the Mira monitor met the required test results as above. No known pregnancy resulted during the time of treatment.

Figure 2: Ovulation during Chemotherapy

Cycle				Start date			8/1/2021				Couple intention:							Notes:											
				End date			8/31/21				Avoid					Achieve														
Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Bleeding		1	2	2	2	2	2	3	3	3	3	2	2	2																	
Monitor		L	L	L	x	L	L	L	L	L	L	L	P	P	L	L	L	L	L	L				L	L	L	P	P	H	L	L
Mucus	H	P	-	-	-	-	-	-	-	-	-	-	-	-	H	H	L	L	H	-				L	L	P	P	H	L	L	L
OPK	N	N	N	N	N	N	P	P	P	P	P	P	P	N	N	N	N	P	N	-				N	-	-	N	P	P	P	P
Mira E3G	218	-	130.9	-	223	70	64	-	58	58	71	40	81	124	112	117	125	234	129	99				77	65	85	57	27	47	37	36
Mira LH	8.42	-	6.8	-	10.7	11	28	-	18	18	22	14	15	15	10	12	10	12	12	11				17	19	24	25	21	38	27	32
Intercourse																															

Cycle				Start date			9/1/2021				Couple intention:							Notes:										
				End date			9/30/21				Avoid			x	Achieve														
Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Bleeding																															
Monitor	-	-	-	L	L	L	L	L	L	L	L	L	L	L	-	-	-	-	-	-	-	-	-	-							
Mucus	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	P	P	L	L	L	H	L	-							
OPK	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-							
Mira E3G	99	36	-	70	-	-	-	65	55	90	108	-	53	152	60	62	38	-	-	-	46	87	120	75			70	99	59	56	
Mira LH	41	42	-	18	-	-	-	24	23	24	25	-	27	24	34	48	19	-	-	-	27	36	37	42			33	37	33	35	
Intercourse																															

Cycle				Start date			10/1/2021				Couple intention:							Notes:										
				End date			10/31/21				Avoid				Achieve														
Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Bleeding																															
Monitor																											L	L	L	L	L
Mucus											L	L	L	L	L	L	L	L	L	L	L	H	L	L	L	P	L	H	L	P	L
OPK																															
Mira E3G	37	79	50	142	62	68	43	-	-	-	x	142	210	184	155	143	236	220	x	x	148	125	200	193	105	250	158	159	252	163	176
Mira LH	55	35	26	33	28	24	21	-	-	-	x	34	22	46	23	18	18	27	x	x	28	20	25	15	9	21	15	16	16	15	16
Intercourse																															

Figure 3: First Menstrual Cycle After Completing Chemotherapy

Cycle				Start date			11/1/2021																								
				End date			11/30/21				Avoid				Achieve																
Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Bleeding																															
Monitor	H	H	H	H	H	-	H	H	H	H	H	H	H	H	H	H	-	H	H	H	H	H	H	H	H	H	H	H	-	H	
Mucus	H	L	H	L	H	P	P	H	H	P	H	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	
OPK																															
Mira E3G	317	202	226	311	136	225	387	272	232	334	-	422	428	>640	-	310	>640	>640	>640	>640	>640	>640	>640	446	>640	>640	540	>640	>640	>640	
Mira LH	27	24	18	13	15	19	33	22	21	19	-	15	9	19	-	7	30	23	17	11	9	15	11	8	6	3	6	7	8	6	
Intercourse																															

Cycle				Start date			12/1/2021				Couple intention:								Notes:												
				End date							Avoid				Achieve																
Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Bleeding																									4	4	4	3	3	3	2
Monitor	H	H	H	H	H	H	H	H	H	-	H	H	H	H	H	H														H	H
Mucus	P	P	P	P	P	P	P	P	P	P	P	P	H	L	H															L	L
OPK											P	N	N																		
Mira E3G	>640	>640	>640	534	576	475	498	>640	>640	>640	>640	>640	470	301	342	452														533	338
Mira LH	7	6	10	8	6	4	4	5	4	3	124	37	10	11	10	6														6	5
Proov															N	P															
Intercourse																															

Figure 4: First Completed Cycle Post Chemotherapy

MARQUETTE MODEL Natural Family Planning WHOLE MISSION

Bleeding: 4 = heavy 3 = moderate 2 = light 1 = spotting

Monitor/Mucus: L = low H = high P = peak OPK: N = negative P = postive Intercourse: I = sex

Cycle	1			Start date		12/25/2021					Couple intention:								Notes:												
				End date							Avoid			x	Achieve																
Cycle day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
Date	25	26	27	28	29	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Bleeding	4	4	4	3	3	3	2	2																							
Monitor						H	H	H	H	H	H	H	P	P	H	L	L	-	-	-	-	-	-	-	-	-	-				
Mucus						L	L	L	H	H	L	P	P																		
OPK																															
Mira E3G						533	338	397	250	>640	245	>640	>640																		
Mira LH						6	5	2	1	5	3	6	26																		
Proov PDG																P															
Intercourse																															

Cycle				Start date		1/21/2022					Couple intention:								Notes:												
				End date							Avoid			x	Achieve																
Cycle day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**32**
Date	21	22	23	24	25	26	27																								
Bleeding																															
Monitor						L																									
Mucus																															
OPK																															
Mira E3G						157																									
Mira LH						4																									
Intercourse																															

Discussion:

Both case studies showed that quantitative hormonal monitoring with Mira was helpful for interpreting the menstrual cycle or absence of a cycle during and after use of chemotherapy for treating breast cancer. The first case with the continued high levels of LH and lack of estrogen and progesterone levels indicated that the woman was likely in a state of menopause. This analysis assured her that pregnancy was not possible at this time. Furthermore, if fertility would return the protocol of threshold levels of estrogen and LH would alert her to such a situation.

For the second case the new technology was able to show that she was not fertile (i.e., not ovulating) during the chemotherapy treatments. It also showed the return of fertility and ovulation when she started on the tamoxifen hormonal maintenance treatment. Although the couple struggled with the treatments and with understanding their fertility status and with sexual abstinence, they were able to be successful with avoiding pregnancy and still live with their fertility.

Our next steps will be to establish hormonal norms with the monitor so that we can better recognize deficiencies or deviations from norms with illness or treatments. This will be accomplished with women tracking their hormones with Mira and having them go through serial ultrasound to determine the actual day of ovulation. We also continue to study the hormonal patterns within the postpartum transition to fertility, during the perimenopause transition to menopause, and with various women's health problems such as polycystic ovarian syndrome (PCOS) and endometriosis.

We continue to conduct multi-situation studies with use of the Mira monitor—postpartum, perimenopause, PCOS, cancer, and irregular menstrual cycles. With this information we will be able to develop and test protocols that can be used in these various difficult situations to help these women and couples avoid pregnancy.