Jennifer G. Hensley, EdD, CNM, WHNP, and Bonita A. Shviraga, PhD, CNM

Metastatic Choriocarcinoma in a Term Pregnancy: A Case Study

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Abstract

The focus of this article is choriocarcinoma (CC), a rare and aggressive obstetric/gynecologic cancer that occurs once in every 20,000 to 40,000 pregnancies. CC is a form of gestational trophoblastic disease, which is the result of abnormal trophoblastic activity encompassing a spectrum of nonmalignant and malignant disease. Forms of gestational trophoblastic disease include complete or partial mole, invasive mole, CC, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.

Typically asymptomatic, the first symptom of CC in 80% of cases is shortness of breath, indicative of metastasis to the lungs. CC affects women of all ages and can occur during pregnancy, after birth, or even years remote from the antecedent pregnancy. It is highly responsive to chemotherapy, with an overall remission rate greater than 90%. This case study presents the story of a pregnant adolescent thought to have an uneventful pregnancy until metastatic CC at term was diagnosed. Available treatments, outcomes and surveillance for the disease, psychosocial aspects, and implications for nursing care are discussed.

Key words: Chemotherapy; Choriocarcinoma; Gestational trophoblastic disease; Gestational trophoblastic neoplasia.

CC is a rare form of gestational trophoblastic disease (GTD) that can metastasize to both mother and fetus. All forms of GTD have malignant potential; when they are malignant, they become known as gestational trophoblastic neoplasia (GTN). Although virulent, CC is highly responsive to chemotherapy, with an overall survival rate greater than 90% and a disease recurrence rate less than 1%, as shown by Altieri, Franceschi, Ferlay, Smith, and La Vecchia, (2003) in their classic analysis.

CC is an inconspicuous cancer until it metastasizes to affected organs, which then causes symptoms such as shortness of breath from lung involvement. After childbirth, gross examination of the placenta may reveal the CC tumor mimicking a small abruption, although most cases are diagnosed following histological examination. In order to increase awareness of CC, we present an adolescent thought to have had a benign prenatal course until shortness of breath at term led to a diagnosis of metastatic CC.

Overview of GTD/GTN

After fertilization, invasion of the fetal allograft by developed trophoblastic cells into maternal tissues is necessary for placental development. Matrix metalloproteinases, regulated by tissue inhibitors of matrix metalloproteinases, produce a synchronized breakdown of maternal extracellular matrix. Women who develop CC have high expression of matrix metalloproteinases and low expression of tissue inhibitors of matrix metalloproteinases (Singh et al., 2011). The exact cause of CC is unknown, although gene expression is involved. Maternal DNA exerts more control over fetal growth and paternal DNA exerts more control over placental growth (Shih, 2007). It has been suggested that paternal genes turn off maternal tumor suppressor genes, allowing for overgrowth of aberrant trophoblastic growth (Berkowitz, Umpierre, Taylor-Emery, Goldstein, & Anderson, 1986). The spectrum of GTD/GTN is listed in Table 1.

Prevalence and Risk Factors

A worldwide estimate of the occurrence of GTD/GTN is difficult due to its rarity and lack of standardization for reporting and pathohistological techniques (Steigrad, 2003). Histologically, GTD/GTN has been identified subsequent to pregnancy terminations that include ectopic pregnancies, early first trimester abortions, and births at term (American College of Obstetrics and Gynecologists [ACOG], 2012). The reported occurrence of GTN in the United States for ages 15 to 49 years is 0.18/100,000 and 1/25,674 births (Altieri et al., 2003; Lurain, 2010; Smith et al., 2003).

The forms of GTD include complete or partial mole (the most common form), invasive mole, CC, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Two of the most common risk factors for women include

1. maternal age less than 20 years or greater than 40 years and
2. a history of a previous complete hydatidiform mole (Altieri et al., 2003).

Other risk factors include maternal blood type A, paternal blood type O, nonwhite races, nulliparity, extended use of combined oral contraceptives, and cigarette smoking (Altieri et al., 2003). A rare form of familial recurrent complete hydatidiform mole is caused by genetic mutation (Yang, Xiang, Wan, & Yang, 2009).

Table 1: Spectrum of Gestational Trophoblastic Disease/Gestational Trophoblastic Neoplasia (GTD/GTN) and FIGO Stages and Scores

Spectrum of GTD/GTN				
Complete hydatidiform mole	• 15% to 25% risk of developing GTN			
Partial hydatidiform mole	• 5% risk of developing GTN			
Invasive mole	• Local invasion with or without secondary metastatic lesions			
CC	• High malignant potential; may present remote from pregnancy; chemo sensitive			
Placental site trophoblastic tumor (PSTT)	• High malignant potential; may present remote from pregnancy; chemo resistant			
Epithelioid trophoblastic tumor (ETT)	• Rare form of PSTT; may present remote from pregnancy; chemo resistant			
FIGO Stages				
Stage 1 non-metastatic	Disease is confined to the uterus			
Stage 2 low-risk	GTN extends outside of the uterus, but is limited to genital structures (adnexa, vagina, broad ligament)			
Stage 3 low-risk	GTN extends to lungs, with or without genital tract involvement			
Stage 4 high-risk	GTN includes other metastatic sites (liver, spleen, kidney, brain, gastrointestinal tract, mouth)			
FIGO Scores	**0**	**1**	**2**	**4**
Age in years	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion (SAB)	Term	–
Interval from index pregnancy	<4 months	4 to <7 months	7 to <13 months	≥13 months
Pretreatment (β-hCG mIU/mL)	<1,000	1,000 to <10,000	10,000 to <100,000	≥100,000
Largest tumor size	–	3 to 5 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Metastatic sites	–	1–4	5–8	>8
Previously failed chemotherapy	–	–	Single drug	≥2 drugs
Low-risk GTN: score <7; high-risk GTN: score >7. Adapted from ACOG (2012).				

Staging and Scoring of CC

Staging and scoring of the disease is based on the revised International Federation of Gynecology and Obstetrics (FIGO) criteria, which determines treatment and predicts long-term outcomes (ACOG, 2012) (see Table 1).

The disease is considered low or high risk based on scoring:

- Low-risk GTN confers a score < 7 and requires single-agent chemotherapy.
- High-risk GTN confers a score ≥ 7 and requires multiagent chemotherapy, surgery, radiation, or all of these.
- Lurain (2011) found that women with scores ≥12 were less likely to survive after treatment.

Treatment

Chemotherapy is started based on symptoms, gestational age at the time of diagnosis, and FIGO scoring (ACOG, 2012). Single-agent therapy includes methotrexate. Multiagent chemotherapeutic regimes include

1. etoposide, methotrexate and folinic acid, actinomycin D, cyclophosphamide, oncovin (EMA-CO),

Choriocarcinoma (CC) is one form of gestational trophoblastic disease (GTD), the result of abnormal trophoblastic activity.

2. etoposide, methotrexate and folinic acid, actinomycin D, carboplatin (EMA-EP), and
3. vinblastine, bleomycin, carboplatin (VBP).

The addition of etoposide as a chemotherapeutic for high-risk GTN in the 1980s led to better long-term survival rates (Lurain, 2011). However, etoposide presents the risk of a secondary malignancy later in life, which includes acute myelogenous leukemia, colon cancer, melanoma, or breast cancer, as found by Rustin et al. (1996). Women and their providers need to be aware of these risks and monitor for disease in the years following treatment (Lurain, 2011).

Although chemotherapy dosing and life-threatening side effects are under the purview of oncology, obstetrical providers care for the affected woman during the postpartum period, and thus need to understand the disease and its treatment. Reliable contraception is the single most important therapy that can be offered. It is essential that no pregnancy occurs because treatment for GTN is monitored by serum beta-human chorionic gonadotropin (β-hCG) values. If those levels were to go up due to a new pregnancy, treatment plans would be confused, and the woman's life could be endangered. During the postpartum visit, obstetrical providers should be anticipating the side effects of chemotherapy, offering support and encouraging continuation of treatment until remission is achieved. Treatment with methotrexate is more tolerable than treatment with EMA-CO, which can be associated with alopecia, nausea, vomiting, rash, and neutropenia (Lurain, 2011). During the postpartum visit, reliable contraception and encouragement to complete chemotherapy should be discussed thoroughly.

Remission and Recurrence (Relapse) Surveillance

Expected remission rates for low- and high- risk GTN are between 80% and 90%, with excellent 5-year survival rates. Between the years 1998 and 2001, the Surveillance Epidemiology and End Result Program of the National Cancer Institute examined survival rates of women with stage 4 (high-risk) GTN. Survival rates for 1, 2, 3, 5, 8, and 10 years, respectively, were 92.6%, 88.9%, 87.2%, 86.3%, 85.1%, and 83.2% (Kosary, 2007). The calculated rate for recurrence of GTN was 1% for any single diagnosis of GTN, but 25% for two diagnoses of GTN (Altieri et al., 2003). Analysis of 2,657 pregnancies from nine GTD/GTN referral centers revealed women treated with single- and multiagent chemotherapy had pregnancy and fertility outcomes similar to women in the general population that included 76.7% live births, 5.3% preterm births, 1.3% stillbirths, 14.2% miscarriages, 1.8% congenital anomalies, and 7% secondary infertility (Goldstein & Berkowitz, 2012). Overall, women affected by GTN and treated with chemotherapy can hope for remission and a future healthy pregnancy.

After treatment, GTN can result in 1) remission, 2) disease recurrence (relapse), 3) persistence of disease or disease resistant to treatment, or 4) a gynecological malignancy remote from the antecedent pregnancy. The most valuable assessment of the course of the disease is a serum β-hCG value.

The Ongoing Role of Human Chorionic Gonadotropin During Surveillance

Abnormal proliferation of trophoblastic tissue results in serum β-hCG values beyond what is expected for a normal pregnancy. The "red flag" universally accepted as being suspicious for GTD/GTN is a value greater than or equal to 150,000 mIU/mL. Serum β-hCG levels are also measured to score and stage the disease and to monitor response to treatment.

The hCG molecule contains an alpha (α) and beta (β) subunit and multiple variants. Most commercially available tests, both serum and urine, react to more than one variant. After treatment for GTN, hCG molecules exhibit more degradation than after a normal pregnancy, and contain concentrations of free, knicked, and β-core fragment hCG. Also, 3% to 4% of the general population produces nonspecific antibodies that mimic β-hCG immunoreactivity, producing false-positive results (ACOG, 2012). Misinterpretation of serum β-hCG values may lead to a misdiagnosis of GTN relapse and unnecessary retreatment. To avoid this, providers need be aware of two scenarios: 1) quiescent GTN and 2) phantom hCG.

Quiescent GTN

Quiescent GTN is the result of temporarily resistant trophoblastic tissue present after completion of treatment. Persistently low serum β-hCG levels (>5 mIU) may be present for months but should, eventually, become undetectable. Women with suspected quiescent GTN must be followed closely for a rising serum β-hCG level, as 6% to 19% may experience relapse (Berkowitz & Goldstein, 2009).

Phantom hCG

On the other hand, phantom hCG is a false-positive phenomenon that occurs after treatment and is caused

by hCG variants found only in serum specimens. These variants are not excreted in the urine. To avoid a misdiagnosis of relapse or resistant disease, a serum β-hCG value should be compared to a urine β-hCG (ACOG, 2012). If the urine β-hCG is negative, the serum β-hCG is a false positive. This too will prevent unnecessary retreatment.

Case Story

D.L. is a 19-year-old G2P0010 who presented for prenatal care at 7 weeks gestation. She continued with routine antepartum care until she was admitted through the Emergency Department at 39-4/7 weeks gestation with shortness of breath and chest pain. Her diagnosis was shocking to the staff: metastatic CC to the lungs and liver confirmed by chest radiograph, abdominal ultrasound, and pleural fluid cytological examination. The decision by obstetrics and oncology was to induce labor so that mutliagent chemotherapy could be initiated as soon as possible.

After induction of labor, she gave birth vaginally to a viable 8 lbs 5 oz male with Apgar scores of 8 and 9, at 1 and 5 minutes, respectively. Her shortness of breath and chest pain was managed with oxygen and intravenous narcotics during labor and the postpartum. Gross examination of the placenta revealed an encapsulated 4-cm mass that resembled a recent abruption in the midline of the maternal surface. The histological report confirmed CC. Examination of the newborn by neonatology was normal and a serum β-hCG value was < 5 mIU/mL. He was considered unaffected.

Due to the advanced status of her disease, during a 24-hour period, D.L. received a cancer diagnosis, had her labor induced, became a mother, and faced chemotherapy. Lack of insurance resulted in a limited interdisciplinary team approach. She was discharged from postpartum as soon as she was stable to an outpatient cancer facility. Fortunately, as an adolescent, she qualified for pediatric oncology care. By report, her support system was excellent and included the newborn, the baby's father, her mother, and extended family.

Diagnosed with stage 4 high-risk GTN, D.L. was started on multiagent chemotherapy. We did not see her until the 6-week postpartum visit at which time her dyspnea was lessened, had no chest pain, and stated all the tumors, except two on her liver, were gone. Although tolerating chemotherapy well, she was disappointed she could not breastfeed. Both she and the baby's father were "*too scared to have sex*" and chose abstinence over contraception. Reluctant to talk about her feelings, she shared she "*never wanted to go through this again*" and intended on compliance with treatment. She declined professional counseling, citing her support system as sufficient. After 7 months of treatment, she achieved remission. Follow-up for relapse included a serum β-hCG level and chest radiograph for 24 consecutive months and then annually for life. Her son would also require an annual serum β-hCG level for life.

Five years posttreatment, D.L. was seen in the clinic for placement of intrauterine contraception. She had since delivered a second son without CC involvement. She remained in remission and her first son remained unaffected. If not asked what she had been through, she would appear to be any other busy mother of two young children.

Remission

Remission is determined after 27 months with no evidence of disease. This includes

1. chest radiographs free of infiltrates
2. initial and consecutive serum β-hCGs values less than 5 mIU/mL at 1-week intervals for 3 months
3. a total of 24 monthly serum β-hCG values less than 5 mIU/mL.

Recurrence (Relapse)

Any woman can relapse, although women treated for high-risk GTN are at a higher risk (Goldstein & Berkowitz, 2012). Recurrence (relapse) is an increase in serum β-hCG values within 18 months after chemotherapy [median interval = 6.5 months] (Berkowitz & Goldstein, 2009; Ngan, Tam, Lam, & Chan, 2006; Yang et al., 2006). Four factors that increase the risk are 1) higher FIGO scoring; 2) greater than 12 months between diagnosis and treatment; 3) 7 months to achieve remission; and 4) less than two courses of treatment (Yang et al., 2006).

Persistent or Resistant Disease

Persistent/resistant disease is defined as never achieving a serum β-hCG value less than 5 mIU/mL after treatment, and confers a lower survival rate. The 5-year survival rate for women affected by high-risk GTN resistant to chemotherapy, based on data from 1,708 women treated between 1980 and 2004, was 43% (Powles et al., 2007). These women may need radiation and/or surgery.

Cases of CC in the Literature

A literature review was conducted for cases of CC using Google Scholar, PubMed, the Cochrane Library, CINHAL, and UpToDate using the search terms CC, GTD/GTN, and pregnancy. A paucity of newer articles was identified, and the most referenced were older, classic articles. The review revealed that 1) CC is inconspicuous until metastatic; 2) the primary site of metastasis is the lungs, resulting in the symptom of shortness of breath; and 3) the CC tumor may mimic a small placental abruption.

Symptoms and signs of CC are related to disease-affected organs: shortness of breath, hemoptysis, vaginal bleeding, abdominal pain, hematuria, and headaches and/or changes in mental status, which herald metastasis to the lungs (80%), vagina (30%), liver and/or brain (10%) (Goldstein & Berkowitz, 2012). Metastasis to the lungs is most common, but other sites include the kidneys, pelvis, spleen, and gastrointestinal tract.

Fifteen cases of CC mimicking a placental abruption were identified in the literature (Bircher et al., 2011; Christopherson, Kanbour, & Szulman, 1992; Fox & Laurini, 1988; Hallam, McLaren, El-Jabbour, Helm, & Smart, 1990; Liu & Guo, 2006). In some of these cases, prudent birth attendants performed a gross examination of the placenta, and their suspicion of CC and histologi-

Table 2: Nursing Implications for GTD/GTN

Preconception
Age is the number one risk factor associated with development of GTD/GTN (<20 years or >40 years). Women who delay childbearing should be advised. The number two risk factor associated with GTD/GTN is a past history of GTD.
Antepartum and intrapartum
• A serum β-hCG level >150,000 mIU/mL is suspicious for GTD/GTN during pregnancy. • Shortness of breath and hemoptysis may herald pulmonary metastasis of CC. • Abdominal CC may present with an ectopic pregnancy. The placental organ should always be examined, and what appears as an abruption should be considered suspicious for CC.
Postpartum
Continued bleeding past the postpartum period could be due to GTD/GTN.
During treatment and follow-up visits to the obstetrical clinic
• Interdisciplinary coordination of care is important but often lacking. • Couples need help to postpone a future pregnancy for 1 to 2 years with use of reliable contraception during treatment. • Assessment of social support systems is indicated. • Counseling for grief, fear, and anger is essential. Methotrexate is well tolerated, but EMA-CO can cause gastrointestinal toxicity, rashes, alopecia and neutropenia.
In the years that follow
• Metastatic cancer with no known primary site should be suspected as GTN that has developed remote from an antecedent pregnancy. • Women who received etoposide are at risk for secondary malignancies later in life; a good medical history and monitoring for potential signs and symptoms of these cancers is essential. • Women and their partners require ongoing surveillance and support after CC treatment to help emotional healing. • Children of women treated for CC require ongoing surveillance for disease. International Society for the Study of Trophoblastic Disease: www.isstd.org/isstd/book.html. National Cancer Institute: http://www.cancer.gov/cancertopics/types/gestationaltrophoblastic

cal confirmation allowed timely follow-up for disease staging, scoring, and treatment.

Unusual presentations of CC were noted in the literature, confirming its inconspicuous nature until metastatic. Barnes et al., (1981) initially diagnosed viral syndrome until the woman returned with lethargy, left hemiparesis, and papilledema that was caused by CC that had metastasized to the brain. Bailey, Hinton, Ashfaq, and Schorge (2003) identified metastatic CC following removal of an abdominal ectopic pregnancy. Prompt diagnosis and treatment led to remission. Remote from delivery, Liu and Guo (2006) diagnosed metastatic CC in mother and infant who presented with continued vaginal bleeding past the postpartum period and a jejunal mass, respectively. After treatment, both attained remission. Bakyalakshimi, Bharathi, and Ponniab (2013) described relapse of resistant CC that presented as gingival hyperplasia. Despite heroic measures, the woman succumbed to the malignancy. Bircher et al. (2011) described the only case of treatment during pregnancy. After developing severe dyspnea at 22 weeks, the woman was treated with methotrexate. At 25 weeks gestation, she went into spontaneous labor and delivered a live newborn. After multiagent chemotherapy, she attained remission and subsequently delivered a healthy full-term newborn.

Psychosocial Aspects After Treatment

The psychological transition required for a woman and her partner to adjust from having a healthy pregnancy to a cancer diagnosis will require counseling and support (Wenzel et al. 1994; Wenzel et al., 2004). The ability to transition effectively will be more difficult if the loss of a pregnancy at any gestation is feared or real. The anxiety and worry that the newborn may be affected should also be addressed.

Petersen, Ung, Holland, and Quinlivan (2005) conducted a cross-sectional prevalence study of 158 women over a 30-year period using the molar pregnancy registry in Australia. Administration of questionnaires that included the Hospital Anxiety and Depression Scale, Satisfaction with Life Scale, and Sexual History Form 12 revealed depression and sexual dysfunction as the most important adverse effects of GTN and treatment. Themes that emerged from the focus groups included

Expected remission rates for CC are 80%-90%, with excellent 5 year survival rates.

sadness/depression, grief, uncertainty, lost expectations/profound helplessness, anxiety, shock, isolation, fertility concerns, delay in childbearing, and concerns about recurrence and concurrent/subsequent medical conditions. Counseling, support from significant others, and having a subsequent healthy newborn were noted as helping the healing process.

A delay in future childbearing to monitor treatment response to chemotherapy incurs intense emotional feelings for the woman and her partner who may be anxious to start or add to their family. This, in turn, delays the emotional healing that can come with the birth of a subsequent healthy newborn (Petersen et al., 2005). During this time, providers are in a premium position to use their professional expertise to listen attentively and offer advice based on past experiences or information from the literature for both the woman and her partner (Table 2).

Summary

Diagnosis of CC probably will not occur until metastasis causes symptoms of affected organs. The differential diagnosis for unexplained dyspnea during pregnancy or continued bleeding past the postpartum should include GTN (Goldstein & Berkowitz, 2012). After birth, gross examination of the placenta should be conducted. A small placental infarct may mimic GTN and warrant histological examination. Low- and high-risk GTN are highly chemo responsive and, when diagnosed and treated early, lead to high remission rates. We hope this case story raises awareness of the rare, but aggressive, CC.

D.L.'s story has a happy ending. Her shortness of breath and placental tumor, almost a "classic" case of CC, led to a swift diagnosis, early treatment, remission, and a subsequent live birth. In retrospect, we remain haunted by the lack of interdisciplinary team coordination available to her and certainly others who are underinsured. We encourage any provider to be the champion of care consolidation and follow-up should a diagnosis of CC be discovered, and to provide counseling, encouragement, and support to the woman and her family. ✣

Jennifer G. Hensley is an assistant professor at the University of Colorado Denver, Aurora, CO. She can be reached via e-mail at Jennifer.Hensley@ucdenver.edu

Bonita A. Shviraga is a clinical manager at the Aurora Nurse-Midwives, Aurora, CO.

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Dowling, Donna A, PhD, RN
Driscoll, Jeanne Watson, PhD, APRN
Ellett, Marsha L, DNS, RN
Faulkner, Melissa S, DSN, RN, FAAN
Fink, Anne Marie, PhD, RN, CDE
Fowles, Eileen, PhD, RNC
Furdon, Susan, MS, RN, NNP
Gallo, Agatha, PhD, RN, CPNP, FAAN
Gharaibeh, Muntaha, PhD, RN
Giurgescu, Carmen PhD, RN, WHNP
Givens, Susan Rumsey, MPH, RNC, LCCE
Gleeson, Roslyn M, MSN, CNS, RN
Goodrich, Sue Ellen, MSN, RN, C
Gordin, Peggy C, MS, RN,C, FAAN
Gross, Ronda Pomerantz, MSN, RN
Guimei, Maaly, PhD, RN
Haley, Jayne, MSN, RNC
Hamlin, Lynette, PhD, CNM, RN
Hart, Marcella A, PhD, RNC
Hawkins, Jane Evans MSN, RN
Hayman, Laura, PhD, RN, FAAN
Hennessy, Mary Dawn, PhD, RN
Horodynski, Mildred A, PhD, RNC
Huddleston, Kathi, PhD, CNS, RN
Hylton-McGuire, Karen, MSN, RNC, IBCLC
Jamerson, Patricia, PhD, RN
James, Dotty, PhD, RN
Jenkins, Ruth L, PhD, RN
Johnson, Merrilyn O, PhD, JD, CNM, CNS, RN
Johnson, Teresa, PhD, RN
Jonsdottir, Sia, MS, CNM, RN
Karahuta, Annette, MSN, RN
Kavanaugh, Karen, PhD, RN, FAAN
Kavinsky, Beth, MSN, RNC, IBCLC
Keefe, Maureen, PhD, RN, FAAN
Kelly, Michelle M, PhD, CRNP
Kenner, Carole, DNS, RNC, FAAN
Khalaf, Inaam Abdullah, PhD, RN
Knowles Susan G, BSN, RNC, CCAP
Kobler, Kathy, MS, APRN, PCNS-BC, CHPPN
Kowalski, Karren, PhD, RN, FAAN
Krowchuk, Heidi vonKoss, PhD, RN, FAAN
LeBon Gort, Danielle, MSN, RN
Lewis, Judith, PhD, RN, WHNP-BC, FAAN
Limbo, Rana, PhD, RN, FAAN
Lindberg, Claire E, PhD, RN, CNS, NPC
Lindeke, Linda L, PhD, CNP, RN
Lipman, Terri, PhD, CRNP, FAAN
Little, Cindy, PhD, RNC, WHNP, BC, CNS
Lockridge, Terri, MS, RNC
Logsdon, Cynthia M, DNS, ARNP, FAAN
Lowenkron, Ann Herman, DNS, RN
Lund, Patricia Z, EdD, RN
Lyndon, Audrey, PhD, RNC, FAAN
Mallory, Debra Luegenbiehl, PhD, RNC
Mandleco, Barbara, PhD, RN
Mattson, Susan, PhD, RNC, FAAN
McCartney, Patricia R, PhD, RNC, FAAN
McCook, Judy, PhD, RN
Mendler, Victoria M, MSN, RNC, WHNP
Miklush, Lisa, PhD, RN
Moos, Merry-K, MPH, FNP, FAAN
Morin, Karen H, DSN, RN, FAAN
Oweis, Arwa, DNSc, RN
Patrick, Thelma E, PhD, RN
Pelzer, Gay D, JD, RN
Pehora, Carolyne, MN, BNcN, RN
Rentschler, Dorothy, PhD, RN
Rohan, Annie J, MSN, RNC, NNP/CPNP
Sanchez, Ana C. Birkhead, PhD, RN, WHNP, BC
Schiffman, Rachel, PhD, RN, FAAN
Schmidt, Cindy, PhD, RN, FAAN
Segre, Lisa, PhD
Semelsberger, Carrie, MS, RNC, NP
Sharp, Kathleen T, MSN, RNC, CRNP
Sharts-Hopko, Nancy C, PhD, RN, FAAN
Shocksnider, Julie, MS, APN, RNC-HROB, CCE
Simpson, Kathleen R, PhD, RNC, FAAN
Slusher, Ida L, DSN, RN
Snelgrove, Erna, PhD, RN
Spear, Hila, PhD, RN, IBCLC
Sterling, Yvonne M, DNSc, RN
Strodtbeck, Frances, DNS, NNP, RN, FAAN
Sudia-Robinson, Tanya, PhD, RN
Susczynski, Sinead, MS, RN, NP
Thoyre, Suzanne M, PhD, RN
Tillett, Jackie, ND, CNM, RN
Vincent, Janice L, DSN, RN
Wambach, Karen A, PhD, RN
Woodgate, Roberta, PhD, RN