BC WOMEN'S HOSPITAL+ HEALTH CENTRE
An agency of the Provincial Health Services Authority

APPENDIX 1:
Literature Summary for
LACTATION SUPPRESSION TREATMENT FOR POST-PARTUM WOMEN

INTRODUCTION

Cabergoline is a dopaminergic ergoline derivative that directly stimulates D2-dopamine receptors on pituitary lactotrophs, resulting in the inhibition of prolactin secretion. This drug has been used clinically for the suppression of lactation and is currently approved by Health Canada for this indication. Cabergoline is currently on formulary at BC Women's Hospital. Cabergoline can be considered for use in the postpartum management of HIV positive women who deliver at BC Women's Hospital to inhibit lactation as well as for the use in other appropriate situations such as for women who have had a stillbirth or second trimester termination or whom are taking medications contraindicated in breastfeeding.

INDICATIONS AND GENERAL TREATMENT RECOMMENDATIONS FOR LACTATION SUPPRESSION

There are well known advantages to breastfeeding however there are instances when avoidance of breastfeeding is required, including newborn illness or death, infant adoption, and maternal illness, such as HIV infection. Breast-milk transmission of HIV accounts for up to 30% of all cases of perinatal HIV infections (Dunn et al, Lancet 1992;340:585-8) and while the risk of transmission is significantly reduced when nursing mothers receive ongoing combination antiretroviral therapy, HIV transmission has been reported despite undetectable viral load in maternal serum and breast milk (Bitnun et al, Can J Infect Dis Med Microbiol 2014;25(2):75-7). In Canada, where safe alternatives to breast milk are available, exclusive formula feeding is recommended for all infants who are born to HIV-infected mothers regardless of maternal HIV viral load (Money et al, J Obstet Gynaecol Can 2014;36(8):721-34).

Physiologic cessation of lactation will occur in the absence of physical stimulus. However before lactation ceases, non-breastfeeding women may experience moderate to severe pain and engorgement (Spitz et al, Am J Obstet Gynecol 1485-90). During this time women may also experience emotional distress due to feelings of personal guilt as well as social and cultural expectations associated with not breastfeeding. Additional concerns in HIV positive women may also be worries about disclosure of HIV infection. It is thereby necessary that the physical, emotional, spiritual and culturally sensitive needs be considered in women who suppress lactation after giving birth.

In clinical practice a wide range of non-pharmacologic methods are used for immediate suppression of lactation after birth. These include breast binding, expression of breastmilk for comfort, avoidance of unnecessary breast stimulation, application of external agents (e.g., cabbage leaves, cool cloths, ice packs) and options for analgesics for pain. However despite non-pharmacologic strategies, up to one third of women may still experience severe breast pain post partum (Spitz et al, Am J Obstet Gynecol 1485-90). A 2009 Cochrane Review concluded that there was no evidence to indicate whether non-pharmacologic approaches are more effective than no treatment for lactation suppression (Oladapo OT et al, Cochrane Database of Systemic Reviews 2009, Issue 1).

Pharmacologic agents for lactation suppression were commonly employed between the 1930s until late 1980s (Spitz et al). These agents typically included estrogen preparations and the dopamine agonist, bromocriptine. In the 2009 Cochraine Review, both bromocriptine (RR 0.36 95% CI 0.24-0.54) and various estrogen preparations (RR 0. 41, 95% CI 0.29-0.59) reduced the proportion of women lactating compared to no treatment or placebo. There was insufficient evidence to address adverse events of the above treatments in this review. However, due to concern for rebound lactation and serious post-partum side effects, use of both bromocriptine and estrogen preparations is no longer

recommended. Importantly, there is limited published evidence on the acceptability on any of the above approaches, pharmacological or nonpharmacological, for suppressing postpartum lactation in women (Oladapo OT et al, Cochrane Database of Systemic Reviews 2009, Issue 1).

LACTATION SUPPRESSION WITH CABERGOLINE

Cabergoline is a more recently available dopamine agonist. It is commonly used in the management of pituitary prolactinomas, and has a Health Canada indication for the prevention of physiological lactation in the puerperium for clearly defined medical reasons (Dostinex® Product Monograph, Kirkland, Quebec: Pfizer Canada Inc. July 2013). Compared to bromocriptine, cabergoline has similar efficacy at inhibiting lactation, with associated advantages of easier dosing, fewer serious side effects, and fewer drug interactions.

- Cabergoline directly stimulates D2-dopamine receptors on pituitary lactotrophs resulting in inhibition of prolactin secretion. It does exert a central dopaminergic effect via D2-receptor stimulation at oral doses that are higher than those effective in lowering serum prolactin levels. Cabergoline has low affinity for D1-, alpha-1, alpha-2 adrenergic and serotonin receptors. Cabergoline has no effect on the basal secretion of other anterior pituitary hormones (GH, FSH, LH, corticotrophin, TSH) or cortisol.

- Cabergoline is well-absorbed with peak concentrations achieved within 0.5 – 4 hours and can be administered with or without food. Tolerability is however improved when given with food.

- Cabergoline is given as a single 1 mg dose (2 x 0.5 mg tab) during the first day postpartum. Onset of effect occurs within 3 hours of administration and the duration of effect lasts up to at least 14-21 days in puerperal women.

- Cabergoline is moderately bound to plasma proteins (41%) and has a long elimination half-life (63-69 hours). It is extensively metabolized via hydrolysis into inactive metabolites. It is not metabolized by the CYP P450 enzyme system and does not cause CYP P450 enzyme inhibition or induction. No known dose reductions are required for mild or moderate hepatic dysfunction however there are limited data in individuals with severe hepatic insufficiency. No dose reductions are required in renal insufficiency.

- Cabergoline should not be used with other drugs that have dopamine agonist activity (e.g., other ergotamines), which could theoretically increase potential effect. It should also not be used with other drugs with dopamine antagonist activity (e.g., metoclopramide, phenothiazines) which may reduce the prolactin lowering effect. Because cabergoline is not metabolized through the CYP P450 enzyme system it is not expected to have other significant drug interactions.

- Cabergoline was well tolerated in clinical trials when used as a single dose for suppression of lactation. Most reported side effects were transient and mild to moderate in severity. Side effects most frequently reported included asymptomatic decrease in blood pressure, dizziness/vertigo, headache, nausea, and abdominal pain. The maximal hypotensive effect of a single dose usually

occurs during the first 6 hours after drug intake and is dose dependent both in terms of maximal decrease and frequency.

- Cabergoline is contraindicated if known hypersensitivity (to agent itself, other ergot derivatives or ingredients in the formulation), uncontrolled hypertension, history of pulmonary, pericardial and retroperitoneal fibrotic disorders, anatomical evidence of cardiac valvulopathy.

- Caution is recommended if using in pregnancy-induced hypertension (pre-eclampsia and eclampsia), administering cabergoline with other medications known to lower blood pressure, cardiovascular disease, Raynaud syndrome, gastrointestinal bleeding, or history of psychosis.

CABERGOLINE COST AND AVAILABILITY

- Generic cabergoline is currently on the BC Hospital provincial formulary; with its use restricted to patients at the BC Cancer Agency (e.g., for prolactin producing pituitary tumors) and for the purpose of prolactin suppression.

- Cabergoline is available as 0.5 mg tablets and costs $84.95 per bottle of 8 tablets. The cost per treatment when used for inhibition of lactation (i.e. single oral dose of 1 mg) would therefore be $21.24.

SUMMARY OF CLINICAL TRIAL EVIDENCE – CABERGOLINE FOR INHIBITION OF LACTATION

Cabergoline has been studied in a number of small controlled trials, which have enrolled healthy women who chose not to breast feed for personal reasons. A summary of those published in English is provided below. Abstracts of studies that were published in non-English languages were reviewed however have not been included. (Giorda G et al, Gynecol Obstet Invest 1991;31(2):93-6., Bozhinova S et al, Akush Ginekol (Sofia) 2001;40(4):11-4., Bravo-Topete EG et al, Cir Cir 2004;72(1):5-9., Sentilhes L et al, J Gynecol Obstet Biol Reprod (Paris) 2012; 41(2):167-73., Bracco PL et al, Minerva Ginecol 1997;49:469-73) There are a handful of other trials publish (French, Spanish, Bulgarian, Italian).

1. **Melis GB, Gambacciani M et al. J Clin Endocrinol Metab. 1987;65:541-5. (accessed abstract only)**

In an early study, 17 puerperal women who chose not to breastfeed received either a single oral dose of cabergoline 0.4 mg, 0.6 mg, or placebo, within 2 to 3 days postpartum. Plasma prolactin levels were measured for 5 days after cabergoline dosing. Lactation was prevented in 3 of 7 women who received the 0.4 mg dose compared to 5 of 5 women who received the higher 0.6 mg dose. Prolactin levels were also demonstrated to decrease faster with the higher cabergoline dose (12 hours vs. 24 hours). A moderate blood pressure decrease was reported 3-6 hours after cabergoline administration.

2. **Melis GB et al. Obstet Gynecol 1988;71(3 Pt 1):311-4.**

In a randomized, double-blind placebo controlled dose-ranging study, 32 healthy women (mean age 28 years) who did not want to breast-feed for personal reasons were randomized to receive either a single

dose of cabergoline 0.4 mg, 0.6 mg, 0.8 mg or placebo within 24 hours of delivery. Lactation, as determined by breast tension, breast tenderness and/or milk secretion, was prevented in all 8 women who received 0.6 and 0.8 mg doses, 4 of 8 women who received the 0.4 mg dose and only 1 of 8 women who received placebo. Serum prolactin levels were significantly reduced from baseline starting at day 1 postpartum in all cabergoline groups however the decreases between the different cabergoline doses were not statistically significantly different. There were no adverse events reported in this trial.

3. **Caballero-Gordo A, Lopez-Nazareno N et al. J Reprod Med. 1991;36:717-21.**

In a prospective, randomized, double-blind placebo controlled dose-ranging study, 140 healthy women were randomized to receive a single dose of cabergoline 1.0 mg, 0.75 mg, 0.5 mg (40 women in each group) or placebo (20 women) within 24 hours of delivery. Complete inhibition of lactation, as determined by absence of milk secretion and/or breast engorgement, occurred in 36 women (90%) who received 1 mg, 25 women (63%) who received 0.75 mg, and 18 women (45%) who received 0.5 mg of cabergoline compared to 4 women (20%) who received placebo. Serum prolactin levels decreased significantly in all women who received cabergoline but the decreases were not statistically significantly different between doses. Adverse effects including dizziness and headache, occurred in four women receiving cabergoline between days 1 and 3 after the dose.

4. **Giorda G, de Vincentiis S et al. Gynecol Obstet Investig. 1991;31:93-6.**

In a single-blinded randomized controlled trial, 36 women were given either a single dose of cabergoline 1 mg or bromocriptine 2.5 mg twice daily for 14 days within 50 hours after delivery. Maximum serum prolactin decreases were similar between groups; 90% decrease with cabergoline by day 5 and 87% decrease with bromocriptine by day 3. Inhibition of lactation, as determined by lack of milk secretion, breast tenderness and engorgement was similar between groups; with complete lactation suppression in 17 women (94%) receiving cabergoline and 16 women (89%) receiving bromocriptine. Reported adverse events included headache, dizziness and vomiting, and were numerically fewer in number with cabergoline than with bromocriptine.

5. **European Multicentre Study Group for Cabergoline in Lactation inhibiton. BMJ 1991;302(6789):1367-71.**

This was a prospective, randomized, double-blind parallel group, multicenter study that enrolled 272 healthy women (mean age 28 years, 61% multiparous) who chose not to breast feed for personal or medical reasons. Women were excluded if they had a history of agalactia or hypogalactia, drug allergy, intrauterine fetal death, pre-eclampsia, liver or kidney impairment, or any concomitant acute diseases. Women were randomized to receive either cabergoline 1 mg single dose or bromocriptine 2.5 mg twice daily for 14 days. The first dose was given within 27 hours after delivery. The primary outcome in this study was treatment success as measured by absence of milk secretion, breast engorgement or breast pain during the first 2 weeks postpartum. This study found that cabergoline was non-inferior to bromocriptine for complete (78% vs. 69%) and partial (15% vs. 24%) success of lactation inhibition. Rebound breast symptoms were significantly lower in cabergoline treated women (5% vs. 24%). Prolactin concentrations decreased significantly in both groups, however the reduction was more rapid in the cabergoline group and rebound lactation was more common with bromocriptine on days 15 and 21. There were numerically fewer adverse events reported in the cabergoline group (18%; 25 events reported among 22 women) than the bromocriptine group (26%; 44 events reported among 36 women), however

differences were not statistically significant. The majority of adverse events occurred on the first day and were considered mild-moderate in severity. The most frequently reported were dizziness, headache, nausea and epigastric pain. There were no significant differences in blood pressure or heart rate changes between groups. Measured orthostatic hypotensive changes were reported in 29 women (10 cabergoline, 19 bromocriptine), with symptoms associated with these changes reported in 14 women (4 cabergoline, 10 bromocriptine).

6. **Nisha S, Uma S, Vineeta S. J Obstet Gynecol India 2009;59(2):152-55)**

Randomized controlled trial conducted in India which enrolled 196 healthy postpartum women (mean age 26 years, 57% mulipara) who needed inhibition of lactation due to stillbirth or neonatal death. Women were randomly assigned to either single dose of cabergoline 1 mg if there was no milk output at the time (n=54) or 0.25 mg twice daily for two days if there was presence on milk output (n=46) vs. a single intramuscular injective of an estrogen-androgen combination (n=96, 48 lactation inhibition, 48 lactation suppression) which could be repeated for a maximum of 3 doses if milk expression continued. In all groups, the first dose was given within 24 hours of delivery or neonatal death. Complete inhibition of lactation was achieved in all women (100%) and 47 of 48 women (98%) of women receiving a single dose of cabergoline and the androgen-estrogen combination respectively. The mean number of days required for inhibition of lactation was significantly lower in the cabergoline single dose group compared to the estrogen-androgen combination group (0.73 vs. 1.81, p=0.001). However, when required for suppression of existing lactation, there were no differences between the carbergoline multi-dose vs. estrogen-androgen groups (3.29 vs. 3.96 days, p=0.244).

EXPERIENCE OF POST-PARTUM CABERGOLINE USE FOR LACTATION INHIBITION IN HIV POSITIVE WOMEN

Buhendwa L et al. Trop Doc 2008;38:30-2.

In an observational study conducted in resource limited setting of rural Malawi, 104 HIV positive women (mean age 26 years, median parity 4) who chose to avoid breastfeeding were offered a single oral dose of cabergoline 1 mg after delivery in order to avoid engorged and lactating breasts which was thought to be culturally unacceptable. Women were not eligible for inclusion if they had a history of hypersensitivity to ergot alkaloids or bromocriptine, toxemia of pregnancy or essential hypertension. Thirty-one women (32%) in this study had past experience with other methods of breast milk suppression, which included traditional medicine, breast compression, or both. Acceptability and effectiveness of cabergoline for inhibition of lactation was assessed through patient questionnaires throughout the first 3 days postpartum. Results were available for 98 women in this study. All women considered cabergoline effective and the maximum time required for breast milk suppression was 1 day. Ninety-three percent of women reported they chose to avoid breastfeeding in order to avoid infecting their baby with HIV, while 67% reported that if cabergoline were not available they would chose to breastfeed because they might end up with mixed feeding due to social pressure as a result of engorged breasts. All of the women preferred that cabergoline be routinely available. Adverse events were reported in 4 women including dizziness (n=2) and epigastric pain (2).

Pammi M et al. Int J STD AIDS 2012;23:280-1.

A National Survey was administered in the UK to evaluate the current knowledge and postpartum practices of physicians providing care for HIV-positive pregnant women. In this study, 167 paper-based questionnaires were sent to genitourinary medicine clinics involved in care of HIV patients and 85 surveys were return (51% response rate). Survey results found that 100% (n=85) of physicians advised HIV positive women to avoid breastfeeding with 93% (n=70) being sure that women did actually avoid breastfeeding. Twenty-three percent (n=17) of physicians routinely prescribed drugs postpartum for lactation inhibition; of which 75% used cabergoline. Thirty-three percent were aware of one or more natural methods of lactation suppression. Forty-three percent were aware of potential interactions between antiretroviral therapy and dopaminergic suppression agents and 22% indicated the interactions were significant enough to avoid these agents. ***There is no evidence of existing or potential drug interactions between cabergoline and any of the antiretroviral drug therapy medications (see pharmacokinetics discussed above)***

SUMMARY

Recommendations for Inhibition of Lactation in HIV Positive Women

In addition to nonpharmacologic methods to suppress lactation post birth, women should be advised regarding the pharmacologic option with cabergoline for lactation suppression, including its role and potential side effects

- Recommended dose
  - Cabergoline 1 mg (2 x 0.5 mg tab) orally on the first postpartum day

- Potential adverse events
  - Headache, dizziness, fatigue, orthostatic hypotension

- Contraindications
  - Drug hypersensitivity (cabergoline or other ergot alkaloids),
  - Pregnancy induced hypertension (pre-eclampsia, eclampsia)
  - Postpartum hypertension
  - Receiving antihypertensives
  - Pulmonary or cardiac fibrotic disorders

- Precautions
  - Hypotension
  - Raynaud syndrome
  - Liver / Renal disease
  - History of psychosis

- Drug interactions
  - *May exist with antiemetics commonly used in the postpartum period*
  - Dopamine antagonists (metoclopramide, phenothiazines, butyrophenones) – may reduce prolactin lowering effects of cabergoline
  - Other ergot alkaloids