Safe handling of reproductive hormones routinely used in equine practice

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Introduction

The use of exogenous reproductive hormones and/or hormone analogs is a mainstay of both clinical practice and research activities in equine reproduction. The National Institute for Occupational Safety and Health (NIOSH) defines hazardous drugs as those that are known or suspected to cause adverse health effects in people from exposure in the workplace, and reproductive hormones such as those routinely used in equine practice are considered hazardous.[1] Therefore, these agents can have inadvertent deleterious effects on personnel (discussed later), particularly women, who handle and administer them if appropriate precautions are not taken. There are multiple steps during which veterinarians and other veterinary healthcare workers such as veterinary students, technicians and support staff may be exposed to hazardous reproductive drugs including preparing a drug for administration; administering a drug to an animal; and/or during disposal or cleaning of materials used during preparation or administration of a drug (e.g., IV syringes, dose syringes, etc.).[2] Veterinary workers are most likely to be exposed to hazardous drugs via skin contact/absorption, ingestion or inhalation, though needle stick or sharps injuries also pose a risk for inadvertent drug exposure.[2] The objective of this article is to provide an overview of the various formulations of exogenous hormones currently available in the United States for equine reproductive management and discuss personal safety considerations when handling and administering these agents.

Keywords: Exogenous hormone, equine, mare, stallion, personal safety

Exogenous hormone preparations

With the exception of equine follicle stimulating hormone (eFSH) all of the major hormones secreted by the hypothalmic-pituitary-gonadal axis are available as exogenous formulations that are used to regulate physiological and/or behavioral reproductive phenomena in horses (Table 1). Although native gonadotropin releasing hormone (GnRH) is commercially available in aqueous injectable formulations (e.g., Cystorelin®, Merial Ltd., Duluth, GA; Factrel®, Fort Dodge Animal Health, Fort Dodge, IA), their short half-life limits the usefulness of these products in mares; therefore, the potent GnRH analog deslorelin is widely used instead.[3] Deslorelin is primarily used to induce ovulation in mares that are in estrus with a growing dominant follicle (≥30 mm).[4] Administration of deslorelin stimulates the release of luteinizing hormone (LH) from the anterior pituitary gland, which initiates follicular/oocyte maturation and subsequent ovulation approximately 36 to 48 hours after administration. In 2011, a new FDA-approved deslorelin product (SucroMate™ Equine, Thorn BioScience LLC, Louisville, KY) became commercially available, which supplanted the use of compounded deslorelin products that had been used previously.

Human chorionic gonadotropin (hCG) is routinely used to induce ovulation in mares because of its LH-like activity.[5] Like deslorelin, hCG is typically administered to mares that are in estrus with a growing dominant follicle (≥35 mm). The LH-activity of hCG induces follicular/oocyte maturation resulting in ovulation approximately 36 to 48 hours after treatment. Because hCG is a large foreign (non-equine) protein, repeated administration to mares will induce antibody formation against the hCG molecule. Although the development of anti-hCG antibodies has not been documented to interfere with the efficacy of hCG, it has been demonstrated that aged mares (>15 years of age) tend to be less responsive to hCG.[4,5] For mares in which hCG has not reliably induced ovulation, or there is simply concern that a mare will not respond reliably to hCG (i.e., aged mares), the use of deslorelin is generally warranted. In addition to its use in mares, because of its LH-like activity, hCG is also used in male horses as a diagnostic test for the presence of testicular tissue in suspected cryptorchid horses.[6] If testicular tissue is present in these animals, administration of hCG will stimulate synthesis and secretion of testosterone from Leydig cells within the testicular tissue. A typical hCG-stimulation protocol begins

with the collection of an initial blood sample for assessment of the baseline testosterone level that is immediately followed by administration of 6,000 to 12,000 units of hCG IV. Post-treatment blood samples are collected between one and three hours after hCG treatment and again 24 hours after treatment in order to detect a resultant rise in testosterone. Horses with testicular tissue generally have a >four-fold rise in testosterone in one or both post-treatment samples.[6]

Although follicle stimulating hormone (FSH) products are used extensively for superovulation prior to embryo transfer in cattle and other livestock species, the FSH products that are used (e.g., Folltropin®-V, Bioniche Animal Health Canada Inc., Belleville, Ontario, Canada; Pluset®, Minitube of America Inc., Verona, WI) are of porcine origin and have not been reliably efficacious for superovulating mares.[7] For a period of time, an eFSH preparation was commercially available (eFSH, Bioniche Animal Health Inc., Athens, GA) for superovulating mares;[8] however, that product was subsequently withdrawn from the market. As an alternative, a recombinant equine FSH (reFSH) product is currently being evaluated for superovulating mares, but it is not commercially available at this time.[9]

Exogenous formulations of the ovarian steroid hormones estrogen and progesterone are used extensively, both alone and in combination, to regulate and/or treat numerous physiological and pathological reproductive conditions in mares (Table 1).[10,11] Estrogen is administered to ovariectomized mares to induce estrous behavior for breeding shed activities; to spring "transitional" mares prior to administration of dopamine antagonists such as sulpiride to hasten the onset of ovulation; and to non-cycling (or ovariectomized) oocyte or embryo recipient mares to enhance the responsiveness of the uterus to subsequent progesterone treatment. In addition, estrogen may be used as an adjunctive therapy in high-risk pregnant mares, such as those with placentitis. Estrogen in combination with progesterone is routinely used for synchronizing estrus/ovulation in cycling mares and it can be used in postpartum mares to delay estrus/ovulation in an effort to enhance the fertility of foal-heat breeding.[10,11]

Progesterone and the synthetic progestin altrenogest are widely used for reproductive management in both nonpregnant and pregnant mares.[11] These hormones are used to suppress estrous behavior in nonpregnant performance horses and in spring "transitional" mares to hasten the onset of ovulatory activity. In pregnant mares exogenous progestins are used extensively (whether warranted or not) to augment endogenous progesterone levels in an effort to enhance pregnancy maintenance during early gestation (<100 days). Exogenous progestins are also used for maintenance of pregnancy in non-ovulating (or ovariectomized) oocyte or embryo recipient mares that lack an endogenous source of progesterone (until fetal-placental production begins) and as an adjunctive therapy in high-risk pregnant mares, such as those with placentitis or severe systemic disease. As noted above for estrogen products, progesterone in combination with estrogen is routinely used for synchronizing estrus/ovulation in cycling mares and it can be used in postpartum mares to delay estrus/ovulation in an effort to enhance the fertility of foal-heat breeding.[10,11]

In addition to its use in mares, altrenogest has also been administered to stallions to temporarily suppress sexual and aggressive behavior during training and related performance activities. Oral administration of twice the labeled dose (0.088 mg/kg) of altrenogest significantly suppressed reproductive behavior in stallions between two and 18 years of age.[12,13] In contrast, oral altrenogest treatment at the labeled dose (0.044 mg/kg) had only a slight effect on reproductive behavior in mature stallions greater than five years of age.[14] It should be noted however, that in the later study the altrenogest was administered for only 30 days,[14] whereas it was administered for 57[13] and 240[12] days in the two previously cited studies. Additionally, it is important to note that there are limited data on the long-term effects of this treatment on future fertility in stallions (particularly when used in young stallions); therefore, the use of exogenous altrenogest in stallions that will subsequently be used for breeding should be pursued very cautiously. Exogenous progesterone has also been used empirically to treat self-mutilation behavior in stallions and geldings and anecdotally it has been useful in some of these cases.[15] It is important to diagnose the underlying cause of the behavior in these horses before initiating treatment, because some root causes will not respond to progesterone therapy (e.g., pain-induced self-mutilation).[15]

Although exogenous testosterone and related androgens are not widely used in equine reproduction they are occasionally utilized for behavior/libido modification in stallions with sub-optimal

endogenous androgen levels (Table 1).[16] Compounded injectable preparations of testosterone or long-acting testosterone conjugates have been used for this purpose, and more recently transdermal delivery has been used by applying testosterone in oil to hairless skin in the perineum or directly on the shaft of the penis.[16] When exogenous testosterone is used in stallions it is important to monitor pre- and post-treatment androgen levels in order to avoid an excessive negative feedback effect of the exogenous testosterone and a subsequent down-regulation of the hypothalamic-pituitary-testicular axis.

Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) has applications in nonpregnant and pregnant mares.[17] Two formulations of $PGF_2\alpha$ are currently available, native $PGF_2\alpha$ (dinoprost tromethamine) or the synthetic analog cloprostenol (Table 1). The most common use of $PGF_2\alpha$ in nonpregnant mares is to induce luteolysis in order to terminate corpus luteum (CL) function and bring mares into heat. More specifically, $PGF_2\alpha$ can be used to abbreviate the normal luteal phase to "short-cycle" mares or it can be used to interrupt an abnormally prolonged luteal phase in order to restore normal cyclical ovarian activity. Although administration of two doses of $PGF_2\alpha$ 14 days apart has been used to synchronize estrus/ovulation, it is not a very reliable way of achieving that goal in mares, so more efficacious methods of estrus/ovulation synchronization are used (e.g., treatment with progesterone and estradiol-17β), which incorporate a single $PGF_2\alpha$ treatment to eliminate endogenous progesterone secretion from a CL. Prostaglandin $F_2\alpha$ is also used in nonpregnant mares for its ecbolic effect to stimulate uterine contractile activity for the treatment of uterine fluid accumulation associated with pathological processes such as persistent mating-induced endometritis. Exogenous $PGF_2\alpha$ will stimulate uterine contractile activity for a duration of four to five hours, with cloprostenol inducing a more consistent response than native $PGF_2\alpha$, so it is the agent of choice for this application.[17] It is important to note, that although historically the CL has been considered to be resistant to the luteolytic effects of $PGF_2\alpha$ until day five after ovulation, it has been demonstrated that CL function is altered following administration of $PGF_2\alpha$ as early as day two after ovulation.[17] Therefore, when using exogenous $PGF_2\alpha$ to treat mares for fluid accumulation during estrus, treatment is generally not continued beyond the day of ovulation. Administration of $PGF_2\alpha$ is the preferred method of terminating pregnancy during early gestation in mares.[17] Prior to approximately 30 to 35 days of gestation, administration of a single dose of $PGF_2\alpha$ is reliably abortifacient through its luteolytic effect causing endogenous progesterone levels to fall below the threshold necessary for continued maintenance of pregnancy. After 35 days of gestation, coincident with formation of the endometrial cups and secretion of equine chorionic gonadotropin (eCG) that induces supplemental CL formation, multiple $PGF_2\alpha$ treatments may be necessary to induce abortion. After fetal-placental production of progesterone/progestins becomes sufficient to maintain pregnancy without an ovarian/CL source of progesterone (>100 days of gestation), $PGF_2\alpha$ can still be used to induce abortion in mares, however multiple treatments will be required over the course of several days.

Although they are not used nearly as extensively as $PGF_2\alpha$, prostaglandins E_1 (PGE_1) and E_2 (PGE_2) do have therapeutic applications in nonpregnant and pregnant mares (Table 1).[17] Topical application of 1.0 mg PGE_1 cream to the caudal cervical os and lumen has been used to induce cervical relaxation to aid uterine fluid evacuation after breeding in mares in which the cervix fails to relax during estrus.[18] Similarly, local application of 2.0 to 2.5 mg PGE_2 into the cervical canal has been performed to aid cervical relaxation (i.e., "cervical ripening") prior to induction of parturition.[19] Cervical ripening with PGE_2 appeared to favor shorter delivery times and foal vigor, although the number of mares in the study was small and most of the end points that were compared between control and PGE_2-treated mares were not significantly different. Intrauterine deposition of PGE_2 prior to insemination has been performed in an attempt to enhance pregnancy rates by increasing colonization of the oviduct by fertile spermatozoa. The primary interest in this treatment modality is for situations involving "low-dose" insemination with a sub-optimal number of spermatozoa. In an initial report,[20] intrauterine deposition of 0.25 mg PGE_2 two hours prior to insemination improved pregnancy rates in mares inseminated with a suboptimal number of spermatozoa from a stallion with good semen quality, but the same treatment did not improve pregnancy rates in mares inseminated with a suboptimal number of spermatozoa from a stallion with poor semen quality; therefore, further studies are needed to more fully assess the benefit (if any) of intrauterine administration of PGE_2 prior to insemination with a suboptimal number of spermatozoa. There is

increasing interest in the use of PGE_2 to reestablish oviductal patency in infertile mares, which is based on work by Allen et al[21] who described laparoscopic delivery of PGE_2 onto the oviducts of 15 chronically infertile mares. The mares were ten to 21 years old and all of them had failed to become pregnant over a period of one to four years during which they were bred to fertile stallions. None of the mares had any identifiable reproductive pathology that would explain their infertility. Laparoscopic application of 0.2 mg of PGE_2 gel onto the surface of the oviducts was performed, and after treatment 14 of the 15 mares (93%) became pregnant either the same or the following year. The authors hypothesized that over time the mares developed blocked oviducts due to the accumulation of naturally occurring collagenous oviductal masses and that topical application of the PGE_2 induced changes in circular and longitudinal oviductal smooth muscle contractility that resulted in the cathartic transport of the masses out of the oviduct into the uterine lumen restoring patency. Although the results are encouraging, the absence of a group of control mares and the lack of pretreatment evidence that oviductal blockage was the underlying cause of infertility in these mares are limitations of the study; therefore, further work is needed to more fully understand the incidence of infertility caused by pathological oviductal blockage in mares and the suitability of laparoscopic application of PGE_2 for its treatment.

The use of exogenous oxytocin has applications in nonpregnant, pregnant and postpartum mares (Table 1).[22] In nonpregnant mares oxytocin has revolutionized the clinical management of endometritis, both persistent mating-induced endometritis and infectious endometritis, because of its ability to stimulate uterine contractile activity and enhance clearance of intraluminal fluid. Depending upon the clinical circumstances, oxytocin can be used alone for its ecbolic effect or it can be combined with large volume uterine lavage to facilitate evacuation of uterine fluid. Oxytocin stimulates uterine contractile activity for approximately 30 to 45 minutes, so repetitive doses are often given during the day in an effort to maximize uterine clearance.[22] A newly described use of exogenous oxytocin in nonpregnant mares is administration during diestrus to disrupt luteolysis to prolong CL function as a means of estrus suppression in performance mares. In the initial report on the use of oxytocin for this purpose, administration of 60 units of oxytocin IM on days seven to 14 after ovulation induced prolonged CL function through day 30 after ovulation in all six treated mares whereas six saline-treated control mares all underwent luteolysis by day 16 after ovulation.[23] In a subsequent report, once daily administration of oxytocin was found to be as effective as twice daily administration for prolonging CL function, which further simplifies the treatment protocol.[24] The primary use of oxytocin in pregnant mares is for induction of parturition and numerous protocols for this purpose have been described.[22] In postpartum mares oxytocin is routinely used as an aid in the treatment of retained fetal membranes. Treatment is generally initiated if the fetal membranes have not been passed within three hours after parturition, and typically consists of administration of ten to 40 units of oxytocin given IV or IM, which may be repeated every 30 minutes to four hours or alternatively given as a slow IV drip diluted in physiological saline. For refractory cases, administration of one liter of lactated Ringer's solution containing 100 to 150 mL of 23% calcium gluconate followed by 20 units of oxytocin IV is often successful.[22]

Personal safety

Given the extensive selection of exogenous hormones that are available and their numerous applications in both mares and stallions it is clear these products are indispensable for the reproductive management of horses. Therefore, it seems inevitable that veterinarians and other veterinary healthcare workers will handle and administer many, if not all, of these agents on a regular basis if they are involved in equine reproductive activities. In addition, veterinarians will likely dispense or provide prescriptions for many of these agents to horse owners, managers or other lay personnel further increasing the number of individuals handling and administering these products. Most, but not all, commercially-available hormone preparations provide specific human safety warnings and guidelines for safe handling and administration (Table 2). In contrast, compounded preparations are generally not accompanied with this type of human safety information (Table 2). Most of the safety warnings that accompany hormone products address particular concerns for women, specifically pregnant women and women of child-bearing age. For example, inadvertent exposure of some drugs (e.g., GnRH analogs and

progesterone/progestins) may lead to disruption of the menstrual cycle; abdominal cramping; increased or decreased uterine bleeding; prolongation of pregnancy; or headaches; while other drugs (e.g., $PGF_2\alpha$, PGE_1, PGE_2 and their analogs) may cause abortion (Table 2). Other safety warnings are more general and are relevant regardless of gender. For example, individuals with asthma or other respiratory conditions, regardless of gender, are urged to use caution when handling drugs such as $PGF_2\alpha$ and its analogs, because they can cause bronchiospasms (Table 2).

A primary emphasis in most of the manufacturer-recommended safety warnings is to avoid direct skin contact since many of the hormones can be readily absorbed through unbroken skin. Because of that concern, most products list specific procedures to follow to avoid direct skin contact such as wearing impervious gloves during drug handling and appropriate hand washing immediately afterwards, particularly if exposure is known to occur (Table 2). In the case of accidental exposure through other routes, most manufacturers recommend seeking medical attention or consulting a physician immediately (Table 2). Although safety warnings are not usually provided with compounded hormone products, it would seem prudent to avoid direct contact with skin by wearing impervious gloves and if contact occurs to cleanse the affected area appropriately, and for other routes of exposure to seek medical attention or consult a physician immediately. Additional information about preventing occupational exposure to hazardous drugs is available through NIOSH.[1,2]

In summary, the use of exogenous reproductive hormones and/or hormone analogs is a mainstay of both clinical practice and research activities in equine reproduction. Although these agents are used to regulate reproductive events in horses, they can have adverse effects on people, particularly women, who handle and administer them if appropriate precautions are not taken. For hormone products that are provided with them, manufacturer-recommended safety warnings should be noted and handling guidelines followed. When specific warnings and guidelines are not provided with a product, such as compounded preparations, heeding safety warnings and handling guidelines such as those that are provided with FDA-approved products and/or following NIOSH guidelines[1,2] would be a judicious course of action.

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Table 1. Exogenous hormone preparations available for equine reproductive management.

Hormone	Product (supplier)	Dose and route(s) of administration to horses	Primary use(s) in horses
Deslorelin acetate (GnRH analog)	SucroMate™ Equine (Thorn BioScience LLC, Louisville, KY)	1.8 mg IM	Induction of ovulation.
Human Chorionic Gonadotropin (LH activity)	Chorulon® (Intervet/ Schering-Plough Animal Health, Summit, NJ)	Mares: 3 to 5 units/kg IV or IM Stallions: 6,000 to 12,000 units IV	Mares: Induction of ovulation. Stallions: Diagnostic evaluation for testicular tissue (i.e., cryptorchid stallions).
Equine Follicle Stimulating Hormone (eFSH)	Commercial product not currently available	NA	When a product was available it was primarily used for superovulation in embryo donor mares.
Estradiol-17β and conjugated estrogens (e.g., estradiol cypionate and estradiol benzoate)	Compounded formulations	See reference #10	1) Induction of estrus behavior in ovariectomized mares. 2) Pretreatment of non-ovulating (or ovariectomized) oocyte or embryo recipient mares. 3) Pretreatment of spring "transitional" mares prior to administration of dopamine antagonists (e.g., sulpiride) to hasten onset of ovulation. 4) High-risk pregnant mares (e.g., placentitis).
Progesterone	Compounded formulations	100 to 300 mg in oil once daily IM or 1.5 to 2.0 grams once every 7 to 10 days for long-acting formulations	1) Hasten onset of ovulation in spring "transition" mares. 2) Estrus suppression. 3) Supplementation of endogenous progesterone in pregnant mares. 4) Maintenance of pregnancy in non-ovulating (or ovariectomized) oocyte or embryo recipient mares. 5) High-risk pregnant mares (e.g., placentitis) or mares with severe systemic illness (e.g., colic/endotoxemia, etc.).
Altrenogest (synthetic progestin)	ReguMate® Solution 0.22% (Intervet/ Schering-Plough Animal Health, Summit, NJ)	0.044 mg/kg orally (0.088 mg/kg in high-risk pregnant mares or those with severe systemic disease)	1) Hasten onset of ovulation in spring "transition" mares. 2) Estrus suppression. 3) Supplementation of endogenous progesterone in pregnant mares. 4) Maintenance of pregnancy in non-ovulating (or ovariectomized) oocyte or embryo recipient mares. 5) High-risk pregnant mares (e.g., placentitis) or mares with severe systemic illness (e.g., colic/endotoxemia, etc.). 6) Suppression of sexual and aggressive behavior in stallions. 7) Treatment for self-mutilation in stallions and geldings.
Progesterone and estrogen combination	Compounded formulations	150 mg progesterone and 10 mg estradiol-17β/day IM	1) Synchronization of estrus/ovulation. 2) Delaying postpartum estrus/ovulation.

Testosterone	Compounded formulations	80 to 100 mg testosterone in oil every-other-day IM or once or twice daily trans-dermal application	Enhancement of libido in stallions.
Prostaglandin $F_2\alpha$ (dinoprost tromethamine)	Lutalyse® (Pfizer Animal Health, New York, NY)	0.01 to 0.02 mg/kg IM	1) Induction of luteolysis. 2) Termination of pregnancy.
Cloprostenol ($PGF_2\alpha$ analog)	Estrumate® (Intervet/ Schering-Plough Animal Health, Summit, NJ)	0.5 µg/kg IM	1) Induction of luteolysis. 2) Termination of pregnancy. 3) Ecbolic for uterine fluid evacuation and/or expulsion of retained fetal membranes.
Misoprostol (PGE_1 analog)	Cytotec® (Pfizer Inc., New York, NY)	1.0 mg topically to cervix	Cervical relaxation in nonpregnant mares.
Prostaglandin E_2 (dinoprostone)	Compounded formulations	2.0 to 2.5 mg topically to cervix or 0.25 mg intra-uterine	1) Cervical "ripening" prior to induction of parturition. 2) Enhanced transport of spermatozoa into the oviduct after insemination.
Prostaglandin E_2 (dinoprostone)	Prepidil® Gel (Pfizer Inc., New York, NY)	0.2 mg topically onto oviduct	Restoration of oviductal patency.
Oxytocin	Many generic formulations	See reference #22	1) Ecbolic for uterine fluid evacuation. 2) Disruption of luteolysis to prolong CL function. 3) Induction of parturition. 4) Treatment of retained fetal membranes.

Table 2. Exogenous hormone preparations available for equine reproductive management and their associated safety warnings regarding inadvertent human exposure.

Hormone	**Product (supplier)**	**Safety warning on product label and/or package insert***
Deslorelin acetate (GnRH analog)	SucroMate™ Equine (Thorn BioScience LLC, Louisville, KY)	Pregnant women and women of childbearing age should exercise caution when handling this product. Accidental administration may lead to disruption of the menstrual cycle. Direct contact with skin should be avoided. INSOLUBLE IN WATER: If direct contact with skin occurs, FIRST wash with alcohol, then soap and water. In case of accidental human injection, consult a physician immediately.
Human Chorionic Gonadotropin (LH activity)	Chorulon® (Intervet/ Schering-Plough Animal Health, Summit, NJ)	No specific safety warning regarding human exposure provided with product.**
Equine Follicle Stimulating Hormone (eFSH)	Commercial product not currently available	NA
Estrogen (estradiol 17β or conjugated estrogens such as estradiol cypionate)	Compounded formulations	No specific safety warning regarding human exposure provided with product.**
Progesterone	Compounded formulations	No specific safety warning regarding human exposure provided with product.**
Altrenogest (synthetic progestin)	ReguMate® Solution 0.22% (Intervet/ Schering-Plough Animal Health, Summit, NJ)	Women of childbearing age should exercise extreme caution when handling this product. ReguMate is readily absorbed through unbroken skin. Impervious rubber or vinyl gloves must be worn when handling ReguMate. Accidental absorption could lead to disruption of the menstrual cycle, abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy or headaches. If direct contact with skin occurs wash immediately with soap and water. For eye exposure flush with plenty of water for 15 minutes and get medical attention. If swallowed do not induce vomiting, call a physician.
Combinations of progesterone and estrogen	Compounded formulations	No specific safety warning regarding human exposure provided with product.**
Testosterone	Compounded formulations	No specific safety warning regarding human exposure provided with product.**
Prostaglandin $F_2\alpha$ (dinoprost tromethamine)	Lutalyse® (Pfizer Animal Health, New York, NY)	Women of childbearing age, asthmatics, and persons with bronchial or other respiratory problems should exercise extreme caution when handling this product. Lutalyse is readily absorbed through the skin and may cause abortion. If direct contact with skin occurs wash with soap and water. [Note: because of its known side effects, it would seem prudent that pregnant women use extreme caution and/or avoid handling this product for veterinary use].

Cloprostenol ($PGF_2\alpha$ analog)	Estrumate® (Intervet/ Schering-Plough Animal Health, Summit, NJ)	Women of childbearing age, asthmatics, and persons with bronchial or other respiratory problems should exercise extreme caution when handling this product. Estrumate is readily absorbed through the skin and may cause abortion and/or bronchiospasms. If direct contact with skin occurs wash with soap and water. [Note: because of its known side effects, it would seem prudent that pregnant women use extreme caution and/or avoid handling this product for veterinary use].
Misoprostol (PGE_1 analog)	Cytotec® (Pfizer Inc., New York, NY)	May cause abortion, pre-term labor or birth defects. No specific handling recommendations provided with product.** [Note: because of its known side effects, it would seem prudent that pregnant women use extreme caution and/or avoid handling this product for veterinary use].
Prostaglandin E_2 (dinoprostone)	Compounded formulations	No specific safety warning regarding human exposure provided with product.** [See note below for Prepidil® Gel formulation of PGE_2].
Prostaglandin E_2 (dinoprostone)	Prepidil® Gel (Pfizer Inc., New York, NY)	Use caution when handling this product to prevent contact with skin. Wash hands thoroughly with soap and water after use. [Note: because this product is used to induce cervical "ripening" in pregnant women, it would seem prudent that pregnant women use extreme caution and/or avoid handling this product for veterinary use].
Oxytocin	Many generic formulations	No specific safety warning regarding human exposure provided with product.**

* See product label and/or package insert for complete details.
** Although no specific safety warning is provided with this product, it would seem prudent to avoid direct contact with skin and if contact occurs to cleanse the affected area, and for other routes of exposure to seek medical attention or consult a physician.