



REVIEW ARTICLE

Traditional Chinese Medicine in the Treatment of Reproductive Disorders of Large Animals in Asia

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ABSTRACT

Reproductive diseases have been a great threat in large animal herds. Before induction of western medicines, traditional Chinese medicine (TCM) that is based on the use of herbal medicine, acupuncture, massage and other forms of therapy has been practiced in China for thousands of years. The foundational text of Chinese medicine dated back to 5th century to 3rd century BCE, humans in China began developing the TCM therapy by maintaining normal homeostasis and body functions. Traditional Chinese medicine prophylaxis is a very different strategy from that of the western medicine, targeting the balance of the diseased animals as compared to the single lesion. Traditional Chinese medicine was also applied to cure ruminant's reproductive disorders such as infertility, abortion and retained placenta. With the increasing concerns of the antibiotic resistance and drug abuse happened, TCM has acquired re-recognition as compared to western medicines due to eco-friendly consumer-driven developments and less residue in food chains. More importantly, a growing number of active substances or extracts with the reliable efficacy are being identified, meanwhile, the quality control measures are satisfied in the large-scale production already. However, few TCM is recognized to be used internationally as the popular human medication. Even less TCM is prescribed legally to animal industry due to poor understanding TCM philosophy and lack of the right guidelines of the registration. This summary aims to elucidate the TCM application in the treatment of the reproductive disorder in large animals and offer alternative strategies for prophylaxis.

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INTRODUCTION

With large requirements for good nutrition across the world, food safety is a growing concern by the public. Asia has been ranked as the largest consumption in global milk production since 2009. However, infertility, miscarriage, stillbirth, dystocia and retained placenta in herds are inevitably recognized as the major diseases, resulting in approximately \$1 billion economic loss per year in USA according to USDA pilot studies (Bellows *et al.*, 2002). Miscellaneous factors are associated with mating, fertilization, gestation, parturition and postpartum recovery (Gilbert, 2016). They include abnormal hormone secretion due to ovary failure and unhealthy endocrine glands. The diseases can also be caused by genetic or congenital abnormalities, infections, tumors, or disorders

of unknown factors. In the sense, reproductive diseases pose a great risk to herd reproduction (Giuliodori *et al.*, 2013). On the other hand, single reproductive disorder may attribute to multiple factors. The conventional approaches not only are the time-consuming and expensive exercise within an evaluation, but also low efficacy by targeting one clinical sign. Moreover, drug residue remains a hazard for food safety (Cerniglia *et al.*, 2016). Principally, it is an urge task to explore an effective approach against reproductive diseases.

Reproductive disorders cannot be triggered by one cause. In fact, lots of subtle effects contribute to the reproduction dysfunction by the systemic disturbance (Cheung, 2011; Grayson, 2011). The TCM philosophy is derived from the tenets of Taoism, Confucianism and ancient Indian philosophy (Tian, 2011). Among these

theories, *yin and yang*, *wuxing*, *zangfu* and *jingluo* are well recorded in Chinese Pharmaceutics. *Yin and Yang* emphasizes the dynamic balance of energy (*qi*) and blood (*xue*); *Wuxing* assigns five basic elements (*fire, wood, water, earth* and *metal*) to different organs or health status, and regulates the balance of body based on their elemental properties (Qiu, 2007). Moreover, *Zangfu* mainly indicates the relationship between general appearance of organs and their function while *Jingluo* is elucidated as channels which maintain the equilibrium of body by regulating energy and blood.

Finally, in the 19th century, western medicine was introduced at the local level by Christian missionary, Hudson Taylor (1832-1905). Compared with the western medicine, herbal ingredients are totally natural origin, less residue and low adverse effect. Raw materials of TCM are widely distributed and grows in Asia, which guarantees rich resources as compared to the chemical products. In addition to natural origin, phytotherapy shares convenient application. Furthermore, TCM prescriptions contain a lot of compositions by targeting multiple organs and improving whole body system. TCM therapy improved 90% cows' estrus and 80% fecundation, respectively (Luo and Gu, 2009). Pregnancy reached to 92% in the treatment group as compared to 26% in the control group post oral administration of Bao Tai San (a kind of TCM herbal formula) combined with the injection of the luteinizing hormone (LH), vitamin E and vitamin A (Wang *et al.*, 2001). A quick discharge of placenta was improved after treatment with the trichosanthin (active substance extracted from root of chinese trichosanthes) (Zhao *et al.*, 2009). In this review, TCM applications are summarized in the cow reproductive disorders except for other herds. All of these prescriptions and acupuncture are recorded for the use against the reproductive diseases in the Chinese Pharmaceutical.

TCM against reproductive disorders

Infertility: Infertility and subfertility are mainly manifested both in male and female livestock. Multiple causes lead to infertility, such as congenital abnormalities, cystic ovaries and persistent corpora lutea, anoestrous, bacteria, protozoan and viral infections (Bittar *et al.*, 2014). Some time, uterine disorders can bring about infertility issues (Bromfield *et al.*, 2015), and nearly 50% postpartum cows will develop metritis and endometritis (Galvao, 2012). On account of the fact, there are limited options to control this disorder effectively. Generally speaking, hormone therapy is a regular mean improving endocrinic conditions, but it is expensive with uncertain therapeutic effects. In view of TCM philosophy, infertility is regarded as deficiency, stagnancy and heat. The deficiency pattern refers to over-consumption of the physical status, too weakness by impairing kidney function. The stagnancy impairs the function of the reproductive organs to response with the hormone secretions. The heat pattern is associated with gynecologic infections, leading to high fever and immune impairment (Lian, 2002). In a few recent studies, innate immune signaling, hypothalamic-pituitary-gonadal axis and infectious factors might involve in the regulative mechanism of the infertility. Traditional Chinese medicine induces ovulation, removes toxic factors of endometrium, and improves the uterus blood flow and estrus by

regulating gonadotropin hormone (Huang and Chen, 2008). Traditional Chinese medicine against infertility was summarize in the following table (Table 1). Male animal infertility, mainly as a problem of small holders and breeding farms, is not discussed in this review.

Miscarriage/abortion: Abortion is abnormal ending of gestation. An abortion which occurs spontaneously is also known as a miscarriage. Infectious diseases and poor management mainly contribute to bovine abortion. Most pathogens are infectious microbes, such as *Brucella abortus*, *Leptospira spp.*, *Bovine herpesvirus 1* (BoHV-1), *bovine viral diarrhoea virus* (BVDV), *Mycoplasma bovis* and protozoan (Anderson, 2007). Additionally, poor management also aggravates the miscarriage (Muller *et al.*, 2015). Once abortion happens, the reproductive failure will occur inevitable and the mother's body will be difficult to recovery. Therefore, abortion cause a negative effect on the economic benefit of herds. Vaccination approach and good management seem to be of high priority in light of the western medicines. However, herd miscarriage is associated with the impairment of the *chong* and *ren* channels according to TCM philosophy. Traditional Chinese medicine *Chong* refers to female endocrine system while TCM *ren* means the function of the uterus and the ovaries. Based on the TCM's syndrome manifestations, miscarriages are classified as three types: deficiency of kidney and spleen, depletion of *qi* and blood, and internal heat due to *yin* deficiency. Therefore, TCM therapy is able to enhance function of uterus, rebalance endocrine disorders and improve maternal immune system by using tonic herbs. Abortion model induced by lipopolysaccharide (LPS) in mice is associated with the upregulation of NK cells and IL-2 expression (Zhong *et al.*, 2002). Apparently, infection involves the harmonia body balance between mother herd and their fetus (Arck and Hecher, 2013; Erlebacher, 2013). Herbal prescriptions with *Radix scutellariae* and *Rhizoma atractylodis* were effective to reduce the abortive cases by lowering IL-2 levels and the NK cells infiltration. Moreover, more survival fetus, high levels of the progesterone and IL-4 were observed post administration with the herb medicines (Tian Shan Pan Shi powder and Bao Tai Wu You powder). These TCMS were beneficial for embryo survival and implantation in dairy cows (Ma *et al.*, 2011). Furthermore, an increasing pregnancy was associated with IL-4 expression and the balance of Th2/Th1 in cows (Ma *et al.*, 2012). Efficacy of *Gloriosa superba L* has been recorded in the treatment of infertility, kidney problems, sexually transmitted diseases, and internal parasites both in India and Africa continents (Kavithamani *et al.*, 2013). More, extracts of the rhizome are applied topically during baby birth to reduce labor pain in India. Later on, colchicine and colchicoid are made from *Gloriosa superba L*. (Veeraiah and Reddy, 2012). In Chinese herb prescription, Bai Zhu San (*Atractylodis macrocephalae*) is able to interfere the miscarriage induced by mifepristone, increase the expression of IL-10 and IL-4 levels in uterine lysates and balance Th1/Th2 secretion (Geng *et al.*, 2014). In comparison with hormone therapy, better embryonic development and higher live fetus were found post administration with herbal medicine alone or combination with progesterone (Yang *et al.*, 2013).

Table 1: Herbal medicines against infertility

Composition	Forms	Application	Efficacy	References
<i>Morinda officinalis</i> , Safflower, Cowherb seed <i>Herba epimedii</i> , Fructus <i>psoraleae</i> Semen <i>cuscutae</i> , Kudzu vine root	Powder	300g per cow, oral administration per day for 8 days, then withdraw for 5 days, subsequently 250g for additional 8 days	90% recovery	He <i>et al.</i> (2012)
Chinese dodder seed <i>Epimedium Herba</i> <i>houத்துயුනිය</i>	Perfusion liquid	50ml for uterine infusion once every 2 days, lasting for 6 days	66.6% efficacy & 50% pregnancy	An <i>et al.</i> (2012)
<i>Epimedium</i> , Actinolite, <i>Astragalus membranaceus</i> <i>Ligusticum wallichii</i> , Semen <i>allii tuberosi</i>	Decoction	One dose, orally administration, lasting for 15 days	90% recovery & 77.8% pregnancy	Liu <i>et al.</i> (2013)
Common <i>cnidium</i> fruit Lightyellow <i>sophora</i> root Rhizome of Chinese goldthread, Licorice	Perfusion liquid	50ml once every 2 days, lasting for 5 days	Cure rate of 8 cows was 100% in a week	Cong <i>et al.</i> (2015)
<i>Radix salviae miltiorrhizae</i> , Rhizoma <i>ligustici wallichii</i> , Rhizome of <i>rehmannia</i> , Root of <i>rehmannia</i> , <i>Radix paeoniae alba</i> , Motherwort	Powder	One dose, oral administration per day, lasting 3 days	77.8% efficacy	Fan <i>et al.</i> (2011)
Deer horn glue <i>Morinda officinalis</i> , <i>Angelica</i> <i>Liquorice</i>	Decoction	1-3 days after the end of the estrus cycle. One dose per cow, orally administration, twice a day, lasting for 3 days	88.9% efficacy	Liu <i>et al.</i> (2014)

Table 2: Traditional Chinese medicine prescription against retained placenta

Composition	Forms	Usage	Efficacy	References
<i>Angelica</i> , Talcum, <i>Rehmannia</i> root, <i>Radix astragali</i> , Tuckahoe, Peach kernel, Motherwort, <i>Radix codonopsis</i> Safflower, Licorice	Decoction	Oral administration one decoction per day	95% success 12h post administration	Chen <i>et al.</i> (2015)
<i>Angelica</i> , <i>Wallichii</i> , Garden balsam, Rhizoma <i>ligustici</i> , <i>Radix codonopsis</i> , Motherwort	Perfusion	Rectal perfusion with 150 ml/per time at 35-40°C, per day	97.8% cure rate and average dosing time was 2.6 times	Li <i>et al.</i> (2015)
<i>Herba Leonuri</i> , <i>Angelicae Sinensis Radix</i> , Flos <i>Carthami</i> , Myrrha, Rhizoma <i>Cyper</i>	Tincture	Oral administration per day, 0.45g herb/kg BW.	73.1% success within 72 h	Cui <i>et al.</i> (2014)
<i>Fructus meliae toosendan</i> , <i>Radix bupleuri</i> , Semen <i>litchi</i> , Fennel Frankincense <i>Notopterygium</i> root	Decoction	0.4g crude herb/kg BW fed directly or put into the feed, twice a day	95% recovery within 4-20 days	Lv <i>et al.</i> (2014)
Garden balsam, Motherwort, Dried ginger <i>Angelica</i> , Peach kernel Safflower, Myrrh Rhizoma <i>cyperi</i>	Tincture	1 ml tincture/ kg BW. orally, once or twice	84.4% cows expelled placenta within 48 h	Cui <i>et al.</i> (2013)
Motherwort, Chinese <i>angelica</i> , <i>Chuanxiong</i> , Semen <i>persicae</i> , Dry ginger Licorice	Powder	250g per cow, orally administration with warm water, once a day, lasting for 3-5 days	No data	Zhou <i>et al.</i> (2010)
Dang Hong Fu	Injection	40 ml extracts or 40g herbs, injected into uterus	83.3% recovery	Luo <i>et al.</i> (2010)

Table 3: Acupuncture points associated with treatment of reproductive disorders in dairy cows

Point	Method	Animal reaction	Indications
Yan Chi	Puncture obliquely lower and backward 6~9cm	Tremble of waist and hips	non-estrus or estrus interrupt
Ming Men	Stab 4.5~7.5 cm	No reaction	delayed ovulation, ovarian
Bai Hui	Stab 6~9 cm	Stoop and tremble of back	atrophy and ovarian dysfunction
Yao Qian	Puncture obliquely lower and backward 12~21cm	Tremble of longissimus and abdominal contraction	
Yang Guan	Stab 4.5~7.5 cm	No reaction	ovarian follicle atrophy, mild endometritis and infertility
Guan Yuan Yu	Puncture obliquely upper and forward 6~7.5cm	Abdominal and intercostal rhythmic contraction	abnormal estrus
Hou Hai	Puncture obliquely upper and forward 10.5~12cm	Tail up and anal contraction	
Shen Peng	Stab 3~4.5 cm	Contraction of lumbar muscle	chronic endometritis, ovarian
Shen Yu	Stab 3~4.5 cm	Contraction of lumbar muscle	cyst and non-estrus
Tian Ping	Stab 4.5~7.5 cm	No reaction	retained placenta
Wei Gen	Stab 6~9 cm	Tail up and anal contraction	
Hou San Li	Puncture obliquely upper and backward 6~7.5cm	Hind limbs disturbance	

Retained placenta postpartum: Retained placenta is also known as the retained fetal membrane or the retained cleansing. It occurs when the fetal membranes fail to separate from the mother. Retained placenta is usually defined as the failure to expel fetal membranes within 24 hr after parturition (Fourichon *et al.*, 2000; Drillich *et al.*, 2006). More important, retained placenta is most commonly associated with dystocia, milk fever (metabolic diseases) and twin births. Both fetal and maternal hormones involve in the reproductive process (Beagley *et al.*, 2010). Higher level of progesterone and lower level of 17 β -E2 might associate with the retained placenta (Weeks *et al.*, 2010). Down-regulation of *Cyp19* gene associated with the estrogen synthesis was reported in the diseased

cows (Ghai *et al.*, 2012). In addition to hormones, immune suppression is a leading cause of the retained placenta (Adrian, 2013), especially by MHC-I mismatch between fetus and mother herd (Benedictus *et al.*, 2013) as well as lower activity of leukocyte in placental tissue. Apart from above causes, weak contraction of myometrium, lesion of cotyledon, edema of villus, heparin released by mast cells and deficiency of trace minerals also involve in the retained placenta (Hehenberger *et al.*, 2015). Antimicrobials and surgical dissection of excess tissue in the pregnant flock are usually recommended as standard treatment. However, it will increase the risk of anesthetic and surgical complications. Conservative treatments are found to be

ineffective. With respect to TCM therapy, retained placenta mainly attributes to the deficiency of *qi* and blood, improper feeding management and oversized fetus. The delivery process consumes too much air and blood, leading to weakness of uterus. Also, blood stasis is attributed to the impairment of *Chong* and *Ren* channel, unbalancing the system of *yin* and *yang* post parturition. Deficiency and cold pattern induce uterine inertia and retention. On contrary to western medicines, TCM can be used to restore the uterus function by promoting blood circulation and improving blood stasis, tonifying *qi* and lifting *yang*. Principally, herbal prescriptions are characterized as antibiosis, antiphlogosis and immunoenhancement as well as fertility improvement without endometrial injuries. Traditional Chinese medicine prescriptions are listed for treatment of retained placenta in the Table 2.

Uterine prolapse: Uterine prolapse (UP) is a relatively common sequela of parturition in beef cattle and dairy cows, characterized by expulsion of part or all of the bovine cervix and uterus. Prolapse of the uterus occurs immediately after or within several hours of parturition, when the cervix is open and the uterus lacks tone. Various predisposing factors are associated with uterine prolapse in the cow, i.e. hypocalcaemia, prolonged dystocia, fetal traction, fetal oversize, retained fetal membranes, chronic disease and paresis (Risco *et al.*, 1984; Potter, 2008). Compared with other postpartum, uterine prolapse is easy to be diagnosed, but difficult to be recovered (Miesner and Anderson, 2008). Conventional therapy includes uterus cleaning and restoration, administration of antibiotics, dexamethasone and oxytocin, and insertion of perivulvar retention sutures (Gardner *et al.*, 1990). However, any delay and improper treatment can result in secondary endometritis, infertility, and even death (Potter, 2008). Traditional Chinese medicine measures of UP have been dated back to 600 AD, Sui Dynasty, China. Uterine

prolapse belongs to deficiency pattern due to the weakness of *qi* and *yang* deficiency. Injury and damage to uterus function contribute to deficiency pattern during parturition (Gao, 1958). The basic therapeutic principle is to tonify kidney, to invigorate *qi* deficiency for the recovery of the prolapsed uterus. Traditional Chinese medicine prescriptions are largely used in treating women's uterine prolapse. However, few of these recipes are applied in beef cattle and dairy cows. Particularly, traditional prescription (Bu Zhong Yi Qi Tang) is now widely applied in dairy cow. Once decoction was administered orally once daily, lasted for 3 to 7 days, the suffered cows had a good prognosis after treatment (Wang, 2014). Although diverse treatments of prolapsed uteri were recorded, no reports have been carried out to compare the efficacy among the different approaches.

Current applications of acupuncture in reproductive disorders:

Animal acupuncture is a critical part of TCM and acupuncture practitioners use the treatment for a wide range of health problems. They believe that energy (*qi*) flows through the body along 14 pathways referred to as Meridians. Along these channels, multiple special sites known as acupuncture points are discovered through practice and experience. Acupuncture points are considered as aggregation of *qi* and blood, which possess unique biophysical reactions. Stimulation of acupuncture points by touching or needling triggers blood circulation, muscle relaxation and neuro-regulation. Therefore, acupuncture is mostly useful to functional disorders, such as downer cow syndrome, paralysis, allergy, respiratory problems, colic and certain reproductive disorders in large animals. In recent years the acupuncture treatment of animals has been all the rage. Acupuncture was proved to be effective of stimulating the blood flow of corpus luteum as well as increasing progesterone level in dairy cows (Ibraim *et al.*, 2015).

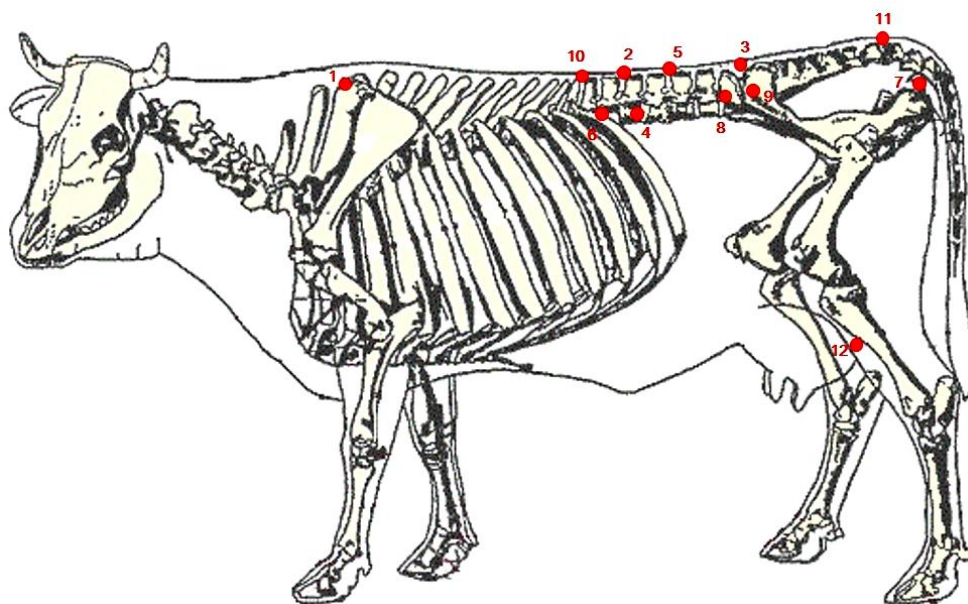


Fig. 1: Acupuncture points associated with treatment of reproductive disorders in dairy cows. 1 Yan Chi (left and right points on each side), 2 Ming Men, 3 Bai Hui, 4 Yao Qian (left and right points on each side), 5 Yang Guan, 6 Guan Yuan Yu (left and right points on each side), 7 Hou Hai, 8 Shen Peng (left and right points on each side), 9 Shen Yu (left and right points on each side), 10 Tian Ping, 11 Wei Gen, 12 Hou San Li (left and right points on each side).

Aquapuncture is a specialized form of acupuncture in which liquid Vitamin B-12 is injected into the regular acupuncture points. Aquapuncture treatment was given the dairy cows at Bai Hui point each time per day, continuously for 3 days, milk production and lesions were improved significantly post infection with mastitis (Daga *et al.*, 2013). Moreover, the herds received aquapuncture with 10 ml of 50% glucose solution at Bai Hui point and 5ml at Shen Peng point for 14 days, the efficacy was 77.7% (14 of 18 cows) in comparison with 30% recovery post treatment with gonadotropin releasing hormone (GnRH) (Lin *et al.*, 2002). The detailed information associated with treatment of reproductive disorders of dairy cows, anatomical location was described in Fig. 1 and Table 3.

Challenges: In comparison with the western medicines, TCM prescriptions still keep the traditional ways (Xu *et al.*, 2014; Guo *et al.*, 2006), such as the rough herbal materials, extracts and the unknown active ingredients. As an evidence-based medicine, each herb medicine is an empirical formula in a long history, which possess randomization and individuality. Even less, herbal ingredients could be replaced by another herb candidate. Consequently, it is too complicated to explain the TCM mechanism in the light of the western medicine. The similar thing happens in daily smartphone industry between Android operating system and IOS platform. In future, TCM philosophy will be elucidated and recognized globally based on animal models. Furthermore, the releasing TCM international standards were noted as a big step for the international standardization of acupuncture field in 2014. The first standard will enhance quality and safety of acupuncture needles and further boost international trade and internationalization of TCM. However, TCM registration is being delayed due to lacking of international recognition and modules across the world. Another challenge still exists in term of the quality consistency and safety of the raw materials. Herbal compositions are diversity due to the seasonal growth, environmental locations, process, storage and extensive use of pesticides (Xu, 2011). A recent survey revealed the contamination of heavy metal (arsenic, cadmium, chromium, lead and mercury) and pesticide residues in herbal materials (Harris *et al.*, 2011; Ma *et al.*, 2011, 2015). The results were comparable to the recent reports in Korea and in India (Kim *et al.*, 2014). Apart from those mentioned, how to eradicate the adulteration business is an urgent challenge for TCM industry (Dhami and Mishra, 2015).

Conclusions: Traditional Chinese medicine have acquired popularity in Asia due to empirical therapy and it is widely applied as treatment against reproductive disorders in large animals. With the better understanding of potential mechanism, TCM strategy will be elucidated and accepted internationally and it may play a major role in the prophylaxis of the reproductive diseases in large animals.

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and YXG gathered information and relevant data; ZHZ wrote the manuscript. All authors critically revised the manuscript for important contents and approved the final version.

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