Journal of Fertilization: In vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology

Abraham, JFIV Reprod Med Genet 2017, 5:2
DOI: 10.4172/2375-4508.1000203

Review Article

An Overview on Functional Causes of Infertility in Cows

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Abstract

Although problems in animal breeding are innumerable, infertility is one of the major bottlenecks in livestock production. In this paper functional causes of infertility like luteal deficiency due to abnormal pattern of LH pulses, cystic ovarian disease, and ovulatory defects, persistent corpus luteum, infertility associated with anestrus, non-detected estrus and repeat breeder are presented with respect to cow. It has been documented that in the management of cow, there are many times when the manipulation of normal cyclic activity ensures optimum production or is convenient for the owner by use of hormones to manipulate ovarian cyclic activity. Epitomizing under the prevailing condition increased productivity of the cow can only be achieved through success in minimizing infertility problems associated with functional cause through early diagnosis and treatment in addition to improvement of animal nutrition, health and genetic makeup.

Keywords: Cow; Diagnosis; Hormone; Infertility; Treatment

Introduction

Reproductive performance is one of the most important factors affecting dairy farm profitability and the development of national economy, as well as the living standard of rural and urban societies, Because, it directly or indirectly influences the yield of milk, reproductive culling rate and the cost for breeding and calf sales [1]. Dairy cows should calve one time every year to maximize economic efficiency. Cows that have been highly selected for milk production in recent decades have suffered a decline in cow fertility, fertility is a multi-factorial trait and its deterioration has been caused by a network of genetic, environmental and managerial factors and their complex interactions make it difficult to determine the exact reason for this decline [2].

The ovaries play the key roles in reproduction and any impairment in their functions can result in either sterility or infertility. The term fertility is applied to the cow denotes the desire and ability to mate, the capacity to conceive and to nourish the embryo and finally the power to expel a normal calf and fetal membrane. Sterility means an absolute inability to produce, whereas infertility denotes a degree of reduced fertility which results in failure to produce or delay in producing the normal live calf. Most forms of functional infertility results in anoestrus that means a failure of cows to display estrus [3].

Embryo survival is a major factor affecting production and economic efficiency in all systems of meat and milk production by ruminants [4]. In beef cattle, estimates indicate that fertilization rate for oocytes is 90%, whereas average calving rates to a single service are between 40% and 55%, suggesting a rate of embryonic/fetal mortality (excluding fertilization failure) of about 35% to 50% [5]. The majority of embryonic loss (70-80%) occurs in the first 3 weeks of pregnancy particularly between days 7 and 16 of pregnancy [6].

Hormones of reproduction are classified in to two groups according to their modes of action; primary hormones and secondary (metabolic) hormones. Primary hormones are involved in various aspects of reproduction, implantation and maintenance of gestation, parturition, lactation, maternal behavior and spermatogenesis. Primary hormones include FSH, LH and prolactin from anterior pituitary gland and oxytocin from posterior pituitary gland. Secondary hormones are necessary for the general wellbeing, metabolic state and growth of the cattle. Permit the full effect of the primary hormones indirectly related to reproduction. Secondary hormones are secreted by the pituitary, thyroid, parathyroid, adrenal cortex, uterus and pancreases. These hormones include Thyroid Stimulating Hormone, Adrenocorticotrophic Hormone, Anti-diuretic Hormone, Human Chorionic-Gonadotrophic Hormone and insulin [7].

Progesterone produced by the CL prevents cyclicity by acting on the anterior pituitary in a negative feedback fashion; therefore, decreasing the release of FSH and LH. It prepares the uterus for reception of fertilized ova and subsequent pregnancy. It also helps the cow maintain pregnancy by suppressing uterine contractions and promoting development of the uterine lining [8]. prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is secreted by the endometrial of the uterus and also affects structures on the ovary, helping to initiate ovulation by causing the demise of the CL, which results in withdrawal of progesterone's negative feedback mechanism. High circulating concentrations of progesterone stimulate the production and release of $PGF_{2\alpha}$ from the uterus [9].

The postpartum period plays a pivotal role in Cow's reproduction. The duration of postpartum anoestrus has an important influence on reproductive performance. During the last few years, several studies have been attempted to treat the prolonged postpartum anestrum in cows by using hormonal treatments such as gonadotropin releasing hormone (GnRH), estrogen, prostaglandin (PG F2α) and progesterone [10-12].

Therefore, the objectives of this paper are:

- To give an overview on functional causes of infertility in cows.
- To highlight treatments for those functional causes of infertility in cows.

Follicular and Hormonal Dynamics during the Estrus Cycle

The estrus cycle is divided into different phases, (follicular phase, estrus, and luteal phase) and is regulated by hormones secreted by the

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Received June 27, 2017; **Accepted** July 31, 2017; **Published** August 07, 2017

Citation: Abraham F (2017) An Overview on Functional Causes of Infertility in Cows. JFIV Reprod Med Genet 5: 203. doi: 10.4172/2375-4508.1000203

hypothalamus (GnRH), anterior pituitary gland (follicle stimulating hormone (FSH) and luteinizing hormone (LH), ovary (estradiol and progesterone), and uterus (prostaglandin F2α (PGF2α). The preceding hormones serve as chemical messengers that travel in the blood to specific target tissues which contain receptors that are hormone specific and regulate the phases of the estrus cycle. The combination of hormone secretion and metabolism (liver, kidneys and lungs) maintain the correct hormonal balance during the follicular phase, estrus, and luteal phase of the cycle. A pre-ovulatory follicle and the subsequently formed corpus luteum are the two primary ovarian structures that regulate the estrus cycle through secretion of estradiol and progesterone, respectively [13].

Proestrus, the first phase of the estrus cycle which is building up phase, during this phase the ovarian follicle (under the influence of FSH and LH) enlarges and begins to secret estrogen, Starts in a day or two of regression of the corpus luteum from the previous cycle. Late in pro-estus the vaginal wall thickens and external genitalia will increase in vascularity in preparation for copulation.

Estrus, the period of sexual receptivity, is primarily initiated by the elevation in estrogens from mature follicles just prior to ovulation. In most cases ovulation occurs within a day or two after the onset of behavioral estrus.

Metaestrus, postovulatory phase dominated by corpus luteum function. During this period serum estrogen decreases and progesterone increases [14].

Functional Causes of Infertility in Cows

As a rule the functional causes of infertility tend to affect individual animals within a herd but in the aggregate they constitute an important cause of infertility; furthermore when they affect a large number of a particular sub group in a herd they frequently reflect some other problem, especially nutrition. Most functional aberrations occur because of some endocrinological abnormality which is frequently difficult to specify even with current methods of hormone assay, particularly when single, spot samples of blood or milk are examined. The abnormalities occur as a result of inherited factors; nutritional deficiencies or excess social influence which may arise from modern husbandry methods, for instance the grouping of large numbers of cows thus interfering with the establishment of a stable social hierarchy; and the stress of production [3].

Some of the common causes are elaborated as follows:

a) Non detected estrus(silent estrus)

b) Anoestrus

c) Ovulatory defects

d) Persistent corpus luteum

e) Cystic ovaries

f) Luteal Deficiency

g) Repeat Breeder

Non-detected estrus/silent estrus

The cow show estrus but there is no one who can follow the cow. After the onset of puberty, cyclic ovarian activity should be maintained continuously through the cow's life except during pregnancy and for a short period in the puerperium. The only way that the herd's man knows that, this is occurring when the sign of estrus at approximately 21 days intervals. It is possible that there are signs but those they one not being observed; in this case it is a management problem [15].

The results of studies of the timing of estrus behavior were inconsistent with simple diurnal patterns and probability should be explained in terms of the periods of times for which cows were left undisturbed by other farm activities. Non-detected estrus can be confirmed by identification of cow's, provision of adequate lighting, heat mount detectors and other aids to the detection of mounting and daily follow up of the cow [16].

Anoestrus

Anoestrus is failure of cows to exhibit overt estrus but is more commonly a problem with estrus detection. Some cows exhibit overt estrus for a very short time, have few mounts or show signs of estrus in the middle of the night making estrus detection in these animals difficult. The estrus detection rate on many farms is less than 50%, being a very limiting factor to reproductive efficiency. Many factors, such as footing, management and milk production level, will affect demonstration of estrus. While these cows are not observed in estrus, they have normal estrous cycles and will respond well to ovulation synchronization programs [17].

True anoestrus: It can be defined as the ovaries may be quiescent and inactive; this is referred to as a true anoestrus. The reasons for the failure of normal activity may be insufficient release or production of gonadotropins to cause folliculogenesis, or it may reflect the failure of the ovaries to respond [18]. Clinical rectal palpation will reveal small ovaries which are usually flat and smooth, absence of corpus luteum, either developing, mature or regressing cow in true anestral will have virtually unchanged ovaries whilst a cow in late dioestrus or early dioestrus (metaestrus) will have a distinctly palpable corpus luteum [19]. Equine chorionic gonadotropin hormone can be used to stimulate ovarian activity, it can induce follicular growth and estrus; at a dose rate of 3000-4500 IU. GnRH, Progesterone and estrogen has been used successfully to treat anoestrus in dairy cows [20].

Sub estrus or silent heat: There may be normal cyclic ovarian activity but the cow is not showing the normal behavioral signs; this is described as sub estrus or silent heat. The first and second ovulations post-partum is frequently not preceded by behavioral signs of estrus and is thus truly 'silent heat'. After the second estrus it is unlikely, that may result in true 'silent heats' to occur. When ovulation occurs in the absence of observed estrus it is more likely to be result of a failure of observation due to the short duration of behavior than to poor detection [3].

Diagnosis of the condition is made on the clinical history and rectal palpation of the genital system, no differentiation can be made from non-observed estrus, since the clinician will be checking for evidence of cyclic ovarian activity as demonstrated by a palpable corpus luteum. Determination of progesterone in milk or blood is a useful aid. In respect of treatment, if a mature corpus luteum is present and the cow is not pregnant, $PGF_{2\alpha}$ analogue followed by fixed time insemination is indicated. If the corpus luteum is at refractory stage double injection of prostaglandin regimen at an 11 day interval be used. Alternatively other progesterone implant could be used followed by fixed time insemination [21].

Ovulatory defects

Ovulation in the cow is a typical since it occurs 10-12 h after the end of behavioral estrus and 18-26 h after the ovulatory LH peak. During estrus and after the end of estrus several follicles undergo development but usually only one or occasionally two, ovulate; the other follicles regress and become atretic. The consequences for fertility of anovulatory defect are two-fold: either the oocyte is not liberated

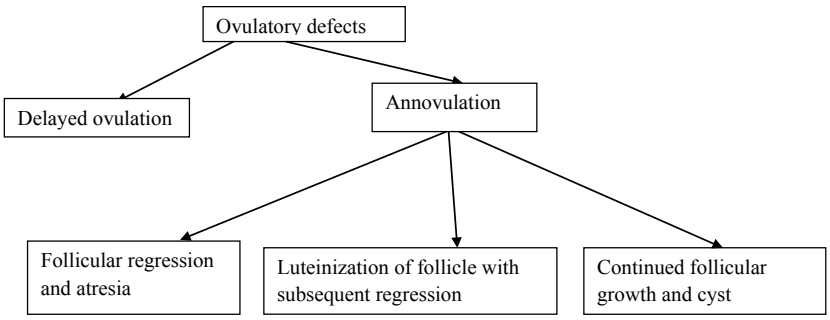

Figure 1: Ovulatory defects [3].

too late so that the spermatozoa are now incapable of fertilization, or else the oocyte has aged and is not capable of normal development. Ovulatory defects can occur due to two causes: endocrine deficiency or imbalance and mechanical factors. It is a complex interaction between ovarian hormones, the anterior pituitary and the hypothalamus. Thus if the quantity of pituitary hormone released is insufficient or its timing is incorrect (this is particularly true of LH), then ovulation is delayed or fails to occur [22] (Figure 1).

Delayed ovulation: The hormone which is important for delayed ovulation is delayed LH surge which plays a big function for the failure of fertilization. If ovulation had not occurred by 24 h after service, the cow should be re-inseminated.

Diagnosis of the condition is difficult since it requires sequential rectal palpation of the ovaries which might self-intervene with of the ovulation and may cause premature rupture. It has been recommended that diagnosis can be made if the single follicle can be detected in the same ovary on two successive examinations, one at peak estrus and another 24-36 h later. Delayed ovulation is generally assumed to be one of the causes of failure of conception in cyclic non breeders [15]. Treatment has consisted of using those hormones that might hasten the timing of ovulation. GnRH Administration causes a rapid rise FSH and LH concentrations peak within 30 to 60 min and return to pre injection values within 4 h. The pattern of release of LH resembles the pre-ovulatory one observed during late estrus in normal cyclical animals [21].

Anovulation: Anovulation has been defined as the absence of ovulation which leads to both true anoestrus or to cystic ovarian disease. Sometimes anovulation is observed before the onset of a period of anovulatory anoestrus with follicle regressing and becoming atretic. If cows are examined per rectum during the first few weeks after calving, a number of enlarged ovulatory follicles can often be detected. They are incorrectly described as being cysts, but they are transient and don't persist even if no treatment is given [23].

Diagnosis of anovulation can only be made retrospectively by noting on rectal palpation or Ultrasonography that a follicle persists longer than one would have suspected .Treatment is directed towards ensuring that ovulation occurs at the next estrus, hence GnRH administered as described or delayed ovulation are indicated [24].

Persistent corpus luteum: Anything that interferes with the production or release of endogenous luteolysin, results in persistent corpus luteum. Pregnancy is the condition which most frequently results in the persistence of corpus luteum, but in the presence of uterine infection and inflammation of the tissues there is interference with the production or the release of luteolysin. There is little firm evidence that persistence of the corpus luteum can occur in the absence of uterine lesions [25].

Cystic ovaries: Ovarian dysfunctions like cysts occur most often during the early postpartum period when there is a transition from the non-cyclic condition during pregnancy to the establishment of regular cyclicity. It is generally accepted that cystic follicles develop due to a dysfunction of the hypothalamic pituitary-ovarian axis. This dysfunction has a multi factorial etiology, in which genetic, phenotypic and environmental factors are involved [26,27]. When discussing the pathogenesis of COF, a distinction may be made between a primary defect in the hypothalamus-pituitary and a primary defect at the level of the ovary in the follicle itself. However, COF formation may result from defects in ovary/follicle and the hypothalamus/pituitary as well [28].

The most widely accepted hypothesis explaining the formation of a cyst is that LH released from the hypothalamus-pituitary is altered: the pre-ovulatory LH-surge is either absent, insufficient in magnitude or occurs at the wrong time during dominant follicle maturation, which leads to cyst formation. It is believed that an altered feedback mechanism of estrogens on the hypothalamus- pituitary can result in an abnormal GnRH/LH release and cyst formation. A GnRH/LH surge occurring prematurely during follicle growth, i.e., when no follicle capable of ovulation is present, can trigger the hypothalamus to be unresponsive to the feedback of oestradiol which results in the formation of ovarian cysts [29].

Follicular cyst: There are several definitions used to describe ovarian follicular cysts and the traditionally accepted definition is that they are "follicular structures of 2.5 cm or larger that persist for a variable period in the absence of a corpus luteum". We can consider ovarian follicular cysts to be any follicular structure on the ovary in the absence of luteal tissue, larger than normal follicular size that persists for a significant period of time and affects the estrus cycle of the animal [30].

Though we cannot determine the exact cause of ovarian follicular cysts, we can recognize that they "develop when one or more follicles fail to ovulate and subsequently do not regress but maintain growth and steroidogenesis" [31]. It has also been determined that follicular cysts are anovulatory structures so, as long as they persist, cow Will remain infertile [30]. Cystic ovarian disease is the "most common endocrine pathology to be found in dairy cows," and incidence is "believed to vary from 1 to 30% depending on herd and breed conditions". Holsteins are the most susceptible to develop a cystic condition compared to other breeds, and the most likely time of diagnosis is 30-60 days after parturition in high-yielding dairy cows [28].

Follicular cysts, when compared to other ovarian cystic conditions,

are characterized by thin walls and produce very small amounts of progesterone. Occasionally, a persistent condition can lead to increased testosterone levels, causing some cows to exhibit masculine aggressive and sexual behavior. However, most cystic cows will remain in anoestrous as long as the condition persists. The fluid in follicular cysts contains many components, including hormones like estradiol, progesterone, and insulin [31].

One proposed explanation for the development of follicular cysts is that "the positive feedback of estradiol on release of gonadotropin-releasing hormone (GnRH) is compromised" [32]. This would not interfere with the ability of the pituitary gland to release luteinizing hormone (LH) in cystic animals, but the overall function of the hypothalamic pituitary- ovarian axis would be altered, and the pre-ovulatory LH surge that normally induces ovulation does not occur. In cystic animals, despite the failure of ovulation by the pre-ovulatory follicle, a surge of follicle-stimulating hormone (FSH) would occur, and under conditions of low progesterone concentrations and high LH concentrations, dominant follicles would be caused to grow to a larger size. These oversized follicles are termed follicular cysts that produce high concentrations of estradiol and inhibin, cause a delay in follicular turnover and are responsible for the persistent cystic condition [32,33].

Luteal cyst: Luteal cystic ovarian disease is characterized by enlarged ovaries with one or more cysts, the walls of which are thicker than those of follicular cysts because of a lining of luteal tissue [34]. Cysts with thicker walls produce high levels of progesterone. In appearance, they are smooth and rounded, with a spherical cavity that is lined by a layer of fibrous tissue surrounded by the luteinized cells [35]. "Luteal cysts are considered anovulatory cysts and are associated with infertility and mucometra in cattle" [24]. When compared to follicular cysts, luteal cysts are more likely to persist over long periods of time and can lead to nymphomania in some animals [36].

Luteal cysts "develop when ovulation fails to occur and the theca undergoes luteinization" [35]. The luteal cyst occurs when the cells of the follicular cyst (granulosa and theca) become luteinized and start producing progesterone. Luteal cyst incidence increases with age and most often affects cows with high milk production [37].

Luteal deficiency: Progesterone is necessary for the maintenance of pregnancy until 150-200 days of pregnancy and perhaps in some cases to term. The main source of the hormone is the CL so that if this is not completely formed or it is not functioning adequately then insufficient progesterone is produced and the pregnancy fails. Luteal deficiencies have been suspected of causing infertility for many years and, although proof is difficult, cyclic non breeders or repeat breeders are frequently treated on this assumption [29].

It is impossible on rectal palpation to differentiate between a normal and abnormal CL; there is a natural variation in luteal size and the position of the CL within the ovary. It is variable and thus makes estimation of its size very difficult. By determining progesterone concentrations in blood or milk it has been possible to make some assessment of luteal function. Arthur et al. [38] found that in 50% of cows that ovulated, yet failed to conceive, the plasma progesterone values six or more days after ovulation were lower than in the group that conceived. Extended low progesterone concentrations during the early luteal phase have been reported in 2% of cows [1] and 18% of cows [19] although some of the individuals which had this pattern conceived. In a study in 91 cow's post-partum the plasma progesterone values during the first dioestrus after calving were 34% lower in 10% of the cows than during the second cycle. In the same study the progesterone levels were similar in both pregnant and non-pregnant cows up to 11 days of the cycle [11].

Repeat breeder: The term repeat breeder or repeat breeder syndrome was created to describe cows that failed to conceive after 3 or 4 inseminations in Cows those are cyclically normal with no clinical abnormalities. Repeat breeder females return to service repeatedly after being bred with a fertile male. The factors which are responsible for these abnormalities are multiple, but the major ones are anatomical, hormonal, managemental and infectious and vary from herd to herd and animal to animals [39]. Repeat breeder cow's exhibit normal signs of estrus every 18 to 24 days but require more than 3 services to become pregnant [40].

In practice, some will have been inseminated at the wrong time, others may have pathological changes in the bursa or oviduct that are difficult to palpate or undiagnosed uterine infections.

Signs of estrus every 18 to 24 days but require more than 3 services to become pregnant [40]. Some of these cases may be associated with early embryonic deaths, failure of fertilization, poor semen quality and most of the embryonic losses in cows occur much earlier in pregnancy than previously believed. Diagnosis of repeat breeder relies on the animal records, rectal palpation, ultrasonography, and vaginal examination [41].

Ovulation is initiated by the increase of the luteinizing hormone (LH), which results in the rupture of the follicle and release of an egg. After ovulation there is a short period during which the egg can be fertilized. Since the period between the first signs of estrus and ovulation occurs at 72 h or later, the cows that ovulate later should be inseminated daily until rectal detection of ovulation is confirmed. Delayed ovulation should not be confused with repeat breeder syndrome (repeat breeders). These cows, if not inseminated daily until ovulation, can also return to service repeatedly after artificial insemination while showing normal signs of estrus every 18 to 24 days.

Treatment of Different Signs of Endocrine Disturbances

Cystic ovarian diseases like follicular cyst is treated with hCG at a dose 3000 to 4500 IU, GnRH at a dose of 100-250 μg for luteinization, at a dose of 0.5 μg for ovulation. GnRH applications more than 80% of the cows come in to estrus within 18 to 24 days. For luteal cyst use Progesterone at a dose of 100 mg in oil intra-muscularly on three consecutive occasions at 48 h interval. $PGF_{2\alpha}$ and its analogue at a dose of 25 mg [30].

Anoestrus is treated with PMSG at a dose of 3000 to 4500 IU to stimulate the ovarian activities and induce follicular growth and ovulation, GnRH at a dose of 0.5 mg to stimulate LH release. But in suckled cows second injection after 10 days is important after transient raise in progesterone to initiate normal cycle [42]

Sub-estrus/silent heat is treated with PGF2α. If there is matured CL, one dose of $PGF_2\alpha$ can stimulate LH secretion, If there is no matured CL, double administration of PGF2α the first dose for maturation of CL and the second for progesterone release [43]. GnRH is the best treatment for ovulatory defects and also it improves pregnancy rate, because it can raise FSH and LH rapidly [3].

Uterine lavage with a PGF2α application and without an antibiotic application may be a preferable treatment method for repeat breeder cows. A gonadotropin-releasing hormone (GnRH) application significantly increases the conception rate in repeat breeders. Therefore, GnRH must be considered in the hormone treatment for repeat breeders [42].

Conclusion and Recommendations

Animal production contributes much to the development of the national economy and to the better living standards of the rural and urban area as well. Reproductive performance is the one that can influence the profitability of the dairy farms in terms of increasing or decreasing milk yield, reproductive culling rate and market price of dairy cows. It can be affected by a network of genetic (hereditary), environmental and managerial factors (malnutrition, lack of intensive follow ups and stress) and their complex interactions.

Functional causes of infertility are secondary to the basic nutritional, hereditary, stress and work factors. As we know the functional causes of infertility usually affect individual animals within a herd but in the aggregate they constitute an important cause of infertility; but in a wide range effect, when this problem affects a large number of a particular group in a herd they frequently reflect some other problem, especially nutritional problems.

Fertility is a multi-factorial character and its deterioration has been caused by those factors listed above. In order to increase the production and productivity, adequate data are required with respect to the functional and also other causes of infertility in cows.

Since the past few years, In order to treat those reproductive aberrations, hormonal treatments and managemental advancements were some of the corrections given by the veterinarians and farm owners to improve the reproductive performance of their animals.

Based on the above conclusive statements, the following recommendations are forwarded:

- Adequate diagnostic facilities for reproductive problems are needed.
- There should be a means for frequent and detailed examination of reproductive organs.
- Awareness among farmers regarding management of reproductive disorders due to nutrition leading to imbalance or inadequate hormonal levels should be created.

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