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Molecular Markers for Fertility in Farm Animals

Review Article

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ABSTRACT

A genetic marker is a gene or DNA sequence with known localization on a chromosome. It can be described as a variation that can be measured or detected by a suitable method, and can be used subsequently to detect the presence of a specific genotype. Such variations occurring at chromosomal or DNA level can serve as genetic markers. The progress in development of molecular markers suggests their potential use for genetic improvement in livestock species. Animal fertility is a measure of reproductive success. In males, it can be defined as the ability of a male to produce semen that will result in a successful pregnancy. In females, it can be defined as the ability of female to cycle and conceive normally to produce a viable offspring. Such a complex feature is under the influence of numerous genes, working together to produce functional gametes, promote early embryonic and fetal development and finally the delivery of a healthy offspring. The heritability is relatively low for fertility so reproductive traits in general are well-suited for application of marker-assisted selection (MAS). Animal fertility is one of the most important economical traits in animal production. Reproductive performance is controlled by the genetic make-up of the female and male, but in general it is largely affected by environment. Phenotypic selection for reproductive traits can only be carried out after puberty while marker-assisted selection could be a tool of choice to improve animal fertility. The possibility of exerting selection criteria at the molecular level shortens the generation interval as the selection decision can take place early in the life of an animal. Moreover, in consideration of the sex-limited nature of reproductive traits, genotypic information could allow for selection in the gender in which the trait cannot be directly observed. Accordingly, there has been considerable interest in mapping and identifying genes involved in the regulation of reproductive traits and in elucidating their expression patterns. The current review aimed to discuss the efforts being made and the approaches currently used in the field of molecular markers and their application to fertility in farm animals.

KEY WORDS farm animal, fertility, molecular marker, QTL.

INTRODUCTION

Reproduction, a process essential to the maintenance of a species, must be under relatively strict genetic control. This control must assure that the steps in the process are repeated with certainty and precision. However, genetic variability exists for several reproductive measures. Genetic variability within breeds suggests that genetic improvement in reproduction is possible. The limited genetic improvement made for reproductive traits has encouraged scientists to search for single genes that may affect reproduction. Recent developments in the area of gene mapping and molecular genetics have now made it possible to search for candidate genes controlling reproductive traits (Seidenspinner *et al.* 2010). Reproductive traits are of primary interest in terms of the economic efficiency of beef cattle production systems (Phocas *et al.* 1998). Sensible financial losses are taken into account when a female does not produce one calf a year, regularly, during the reproductive life and equally have the first parturition at an advanced age (i.e. more than

3 years). Low heritability and lack of information imply a slow genetic improvement of female fertility traits.

Fertility is a very important production trait, but it is difficult to study because it is a complex traitcomprising several component traits and which is greatly affected by differences or changes in the environment, health and nutritional status. Fertility might be considered as two traits which are inherent fertility and expressed fertility. Inherent fertility refers to genetic potential for reproductive performance and is not directly measurable (Moolmuang, 2004).

Genes that affect overall physiological and endocrine functions may control inherent fertility and account for the genetic relationship of measures of early reproductive fitness with growth as well as milk and overall productivity (Meyer *et al.* 1990). Alternatively, expressed fertility can be measured by calving interval, calving rate, service per conception and age of first calving.

During the last decade, a number of tools for genome analysis have been developed for the identification of genes and polymorphism underlying the genetic variation for complex traits including quantitative traits. Detection of polymorphism in the genome of different trait populations can be used to develop the genetic markers that are responsible for specific traits. The presence of these genetic markers in animal genomes can also explain a significant proportion of the variation observed in the trait of interest (Georges, 2007). Both quantitative and genetic markers dominate the theory and practice of animal breeding. Genetic evaluation has started by analysing phenotypes to identify genetic influences, whereas molecular genetics identifies known genotypes via DNA sequences and then examines their influence on phenotypes (Beuzen *et al.* 2000; Gengler *et al.* 2001).

Fertility and Genetics

Maintaining high levels of reproductive efficiency is essential to modern animal production. Several reproductive traits in the female and the male are important. Ovulation rate, uterine capacity and embryo survival are considered as separate female traits. Embryo survival is also under the genetic control of the embryo. Hormone concentrations in the male and female and control of hormone receptors are recent traits under consideration. Genetics play an integral role in the control of these reproductive traits (Rothschild, 1996). Heritability estimates can range from 0 to 1 and are measures of the additive genetic variation that can be manipulated via selection of superior animals within breed or line. Estimates of heritabilities and genetic and phenotypic correlations vary for several reasons including breed studied, method of analysis and sampling variation. Correlations are measures of association between traits and are of particular interest because selection for one trait may adversely affect other traits. High genetic merit cows had higher milk production and reduced reproductive performance compared with medium genetic merit cows (Snijders *et al.* 2001).

Scrotal circumference has been included in the selection index as an indicator trait of male and female reproductive performance (Boligon *et al.* 2010). Negative correlation has been reported between scrotal circumference and age at puberty of both males and females, or either, higher scrotal circumference implies an inferior age at puberty (Martin *et al.* 1992). Positive values of genetic correlation between scrotal circumference and age of parturition were obtained by Morris and Cullen (1994) in European animals. The genetic correlation between growth trait, measured by weight at 550 days, and reproduction trait, measured by stayability (the ability of a female to remain in the herd, producing one calf a year at age of 6 years or more than that age), was very low. This implies that it is possible to control the selection of animals for growing and reproductive traits in a favorable way (Silva *et al.* 2006).

Reproductive performance of the sow exhibits low heritability. Total number of piglets born per litter shows a significantly negative genetic trend. Because of a negative genetic correlation between age at first conception and total number of piglets born per litter (Imboonta *et al.* 2007), It might be possible to improve total number of piglets born per litter by reducing age at first conception. Genetic correlations between reproductive traits of the sow and carcase traits indicate that selection for lean meat growth does also lead to an increase in litter birth weight and average piglet weight at birth (Hermesch *et al.* 2000).

Genetic parameters for reproduction traits including litter size at birth and at weaning, gestation period and litter weight at birth in Boer goats were estimated by Zhang *et al.* (2009), the heritability estimates for all these reproduction traits obtained in the Boer dams are lower than 0.14.

Fertility of dairy cows has continuously declined, especially in the Holstein breed, and mainly after the mid 1980s (Royal *et al.* 2000; Lucy, 2001). Fertility constitutes a major stake for dairy farm since reproductive problems lead to direct and indirect costs. Indeed, many costs were observed as lost income from milk sales due to lesscalves produced per year, an increase in semen costs because of an increase in the number of AIs per conception, costs for treatments and veterinarian or additional costs due to culling of long time infertile animals.

In parallel to the decline of fertility, milk production has continuously increased (Darwash *et al.* 1999; Lucy, 2001). Since milk production and fertility traits are negatively correlated (Berry *et al.* 2003; Flint, 2006), selection of animals for milk yield has been conducted to the detriment of reproductive efficiency (Berglund, 2008).

Subfertility in dairy cows is characterized by changes in traditional breeding and physiological parameters (Royal *et al*. 2000; Darwash *et al*. 1999). Traditional breeding parameters include the decrease in pregnancy rate at first service, the increase in calving-calving interval and calving to first AI interval. Physiological parameters are prolonged postpartum anestrus (the first ovulation is delayed), abnormal estrous cycles (the most common is prolonged luteal phase in the first or subsequent postpartum cycles) or follicular cyst formation. Otherwise, reproductive traits are also largely influenced by environment which plays a key role in determining fertility of the animals. For example, a failure in estrous detection or the misidentification of estrus due to the increased size of herds, the use of semen from sub-fertile bulls or the insemination of cows too early after parturition (Jorritsma *et al*. 2003). Moreover, increasing scientific evidence suggests that diminished oocyte and embryo quality are two major factors in the complex pathogenesis of reproductive failure in dairy cows (Leroy *et al.* 2008 a and b). Oocyte and embryo quality could be affected by negative energy balance (Jorritsma *et al*. 2003; Leroy *et al*. 2008a), but also by genetic factors. Indeed, Snijders *et al*. (2000) collected oocytes from high and low genetic merit cows and observed significantly lower developmental competence in vitro for oocytes of high genetic merit cows. Heritability of female fertility is low, usually less than 5% (Berglund, 2008) but this trait shows high genetic variations (Wall *et al*. 2003). Due to the decline of fertility and its low heritability, a program of detection of Quantitative Trait Loci (QTL) affecting economic traits was carried out by Boichard *et al*. (2003).

Molecular markers

Molecular markers are considered as tools to localize and visualize genetic variation among individuals. They can be used to associate the genetic variation with a trait of interest. The use of DNA markers to define the genotype of animal performance added a powerful tool in animal breeding program improvement (Beuzen *et al*. 2000; Zhao, 2002; Vermerris, 2008).

Niemann-Sorenson and Robertson (1961) were the first to discuss the possible use of blood groups directly in a breeding program. At the DNA level, the types of genetic variation included base substitutions, commonly referred as single nucleotide polymorphisms (SNPs), insertions or deletions of nucleotide sequences within a locus, inversion of a segment of DNA within a locus, and rearrangement of DNA segments around a locus of interest. Through long evolutionary accumulation, many different instances of each type of mutation could be existed in any given species, and the number and degree of the various types of mutations define the genetic variation within a species. The marker types are: restriction fragment length polymorphism (RFLP), single strand conformation polymorphism (SSCP), randomly amplified polymorphic DNA (RAPD), amplified fragment length polymorphism (AFLP) markers, single nucleotide polymorphism (SNP), simple sequence length polymorphism (SSLP), variable number tandem repeat (VNTR), short tandem repeat (STR), restriction site associated DNA (RAD) and microsatellite markers. However, due to the existence of various molecular biology techniques to produce them, and to the various biological implications some can have, a large variety exists, from which choices will have to be made according to purposes. Thus the well-designed studies using these markers will undoubtedly accelerate genes identification involved in quantitative trait loci (QTL) for marker-assisted selection (Vignal *et al.* 2002).

Applications of genetic markers

Evaluation of the genetic diversity

DNA markers are very powerful tools for study of genetic diversity in animals and plant (Karp *et al*. 1997). Farm animal genetic diversity is required to meet current production needs in various environments, to allow sustained genetic improvement, and to facilitate rapid adaptation to changing breeding objective (Kumar *et al*. 2006; EL-Hanafy and Salem, 2009). Genetic characterization and determination of genetic differences between sheep breeds will help in the genetic improvement programs in Egypt (EL-Hanafy and Salem, 2009).

Sexing of pre-implantation embryos

Sex, male or female, is a genetic trait. Gender preselection has a clear application in several fields. Not only is it an important productive tool because it allows the adjustment of offspring gender to market demands, but it also contributes to minimizing gender- linked genetic diseases and might restore a balanced male- female ratio in endangered species. With the development of molecular techniques, the need for quick, reliable, easy to perform method for sex determination can be accomplished using PCR. Different types of PCR including nested, multiplex and primer extension preamplification-PCR (PEP-PCR) have been used to determine the sex of preimplantation IVF-produced embryos in human, bovine, ovine, porcine and buffalo (Gafar and Flint, 1995; Appa Rao and Totey, 1999; Chrenek *et al*. 2001; Fu *et al*. 2007; Darwish *et al*. 2009).

Homologues of a zinc finger protein encoding gene (ZFX: ZFY) have been found on X and Y chromosomes of various animals (Page *et al*. 1987). These have been shown to be evolutionary conserved indicating a functional importance of the gene. However, differences in the X and Y homologue of the gene have been exploited for developing DNA based methods of sex identification in various species. A small region of the ZFX: ZFY loci in buffalo with the prime objective of developing PCR-RFLP based method of sex identification was studied (Pande and Totey, 1998).

Identification of disease carrier

Gene polymorphisms may be considered as genetic markers with potential benefit regarding family counseling and disease management in human (Settin *et al.* 2009) and give a clue about susceptibility or protection from the disease (AL-Tonbary *et al.* 2004).A genetic marker was applied for PCR qualitative assay to detect isolates of Brucella abortus with 100% amplification-efficiency (Asif *et al.* 2009). Also, gene (s) associated with sheep day blindness were detected by Reicher *et al.* (2010) to eradicate the day blindness mutation from improved Awassi flocks. All affected lambs were homozygous for a mutation in the cyclic nucleotide-gated (CNGA3) gene.

Gene mapping

A step towards the use of genomic information in livestock improvement is the location of all markers and protein coding genes in the chromosomes. Thus the development of genetic maps of the species of interest is required for detecting quantitative trait loci using genetic markers (Bovenhuis *et al.* 1997). A recently developed dense map of the horse Y chromosome will provide genes that are expressed exclusively in males and, therefore, have an impact on stallion fertility (Chowdhary *et al.* 2008).

High-resolution gene maps for all chromosomes (autosomes as well as sex chromosomes) have been developed. Though the use of the horse × mouse somatic cell hybrid panels, it had already contributed in a significant way by assigning ~500 markers to various syntenic groups that were mapped to almost all autosomes and the X chromosome (Chowdhary and Raudsepp, 2008).

Markers assisted selection (MAS)

Advances in molecular techniques can now be used to increase rate of response to selection. It has been proposed that candidate gene analysis can be used to identify individual genes responsible for traits of economic importance (Linville *et al.* 2001; Kawahara-Miki *et al.* 2011). Genetic markers provide information about allelic variation at a given locus (Sharifzadeh and Doosti, 2010). The advancement of molecular technology has allowed molecular information to be utilized in selection decisions through marker assisted selection (MAS). Marker assisted selection uses DNA sequences that are associated with a specific trait to supplement phenotypic data used in the quantitative approaches for selection (Parmentier *et al.* 2001). Through marker assisted selection (MAS), animals that are carrying favorable alleles of quantitative trait loci (QTL) can be selected based on a direct evaluation of their molecular biology (Soller, 1998).

Marker-assisted selection (MAS) is best implemented for traits that are lowly heritable and sex-limited (Lande and Thompson, 1990; Soller, 1994). It can also be implemented early in life so that breeders do not have to wait for animal to phenotypically express the trait. Moreover, MAS is most effective for traits that are affected by a small number of genes with large effects rather than with many genes with small effects (Montaldo and Meza-Herrera, 1998; Wikie *et al.* 1999). For reproductive traits, MAS is a promising technique that may aid in genetic improvement due to its low heritability and availability of genetic markers (Drogemuller *et al.* 2001). The technical aspects and potential implications of implementing MAS in livestock, have been depending on successful research for quantitative trait loci detection.

Detection of Quantitative Trait Loci (QTL)

The various genes affecting quantitative traits are individualized by mapping them to specific chromosomal locations (Loci). For this reason, the term quantitative trait locus (QTL) was proposed for the individual mapped genetic factors affecting quantitative traits value (Soller and Lipkin, 2004). Seidenspinner *et al.* (2010) detected quantitative trait loci (QTL) for calving and fertility traits on bovine chromosomes 7 (BTA7) and 10 (BTA10) in the German Holstein population.

The identification of quantitative trait loci (DNA-segment) in selection programmes offers the potential for more rapid improvement, particularly in difficult measured traits. To achieve this potential, there is a need to identify loci having large effects on these traits and the origin of potentially beneficial alleles. With this information, operators of commercial breeding programmes may consider the introgression of positive alleles into their commercial lines, or select for increasing frequency of desirable alleles by within-line marker assisted slection (Ikeobi *et al.* 2002). In cattle, the information of quantitative trait loci that are associated with conformation and functional traits is becoming more readily available (Schrooten *et al.* 2000; Ashwell *et al.* 2005) and traits of lower heritability such as fertility traits, have been successfully mapped for QTL (Boichard *et al.* 2003). QTL are part of the genome showing a preponderant action and explaining the major part of variation of the trait production. Various QTL of female fertility (QTL-F-Fert) were detected measuring the success/failure of each insemination of the daughters of a bull in three French breeds (Boichard *et al.* 2003). A QTL underlying nonreturn rate estimated 90 days after AI in cows and located on bovine chromosome 3 (BTA3), QTL-F-Fert- BTA3, was identified using a sparse 16-microsatellite map in Holstein breed (Guillaume *et al.* 2007). The analysis for this QTL included 2103 AI bulls distributed in twenty-six families. The QTL, finely mapped recently by Druet *et al.* (2008), explained 14% of the total genetic variance (Ben Jemaa *et al.* 2008) and was suggested for acting on fertility events occurring in the first 90 days (Guillaume *et al.* 2007).

Molecular markers for male fertility

Many researchers have generally ignored the male reproductive traits, however, as heritability estimates suggest, selection progress for male traits may be quite effective. A moderately heritable trait which could be measured in the male and which is positively correlated to improve reproduction in the female would be useful in selection to improve female reproductive ability.

Sperm production requires the completion of a complex cascade of events. These steps are mediated by a number of proteins. Consequently, the genes encoding these proteins can be considered as potential candidate genes for male fertility traits (Leeb *et al.* 2005). The availability of genetic markers opens the possibility of detecting fertile and sub-fertile males from one selected line, and of establishing correlations with sperm parameters observed for fresh and frozen semen (Vicente *et al.* 2004).

Male sex determination and development

The first genetic abnormalities that were discovered in infertile patients included sex chromosome aberrations. Humans with 47, XXY karyotype (Klinefelter syndrome) develop into males; however, these patients typically suffer from azoospermia and only very recently some human patients with 47, XXY were discovered that produced little amounts of sperm. Similar chromosomal aberrations also occur in the horse, and a few reports on infertile 65, XXY stallions (Bouters *et al.* 1972; Kubien *et al.* 1993; Kakoi *et al.* 2005) and cattle (Moltenia *et al.*1999) have been published. The earliest signal for male sex determination is produced by the Y-chromosomal SRY gene. Mutations in this gene lead to the development of females with gonadal dysgenesis. SRY mutations have been reported in many species including human 46, XY females (Hawkins *et al.* 1992) as well as female horses with a 64, XY karyotype (Pailhoux *et al.* 1995; Abe *et al.* 1999; Hasegawa *et al.* 2000; Bugno *et al.* 2003). Mutations in the androgen receptor gene (AR) disrupt testosterone signaling and lead to testicular feminization. The molecular nature of this mutation was again first elucidated in human patients (McPhaul *et al.* 1992). Human XY patients with loss of function mutations in the X-chromosomal AR gene develop testes but due to the abrogated testosterone signaling the testes do not descend into the scrotum and these patients develop female secondary sex characteristics. Reports on phenotypically similar cases of horses have been published; however, the molecular defects in these horses were not investigated (Crabbe *et al.* 1992; Howden, 2004). The reported horses resembled mares despite their karyotype being 64, XY. However, they exhibited aggressive stallion-like behavior, were infertile, and upon ultrasonographic examination revealed intra-abdominal testicles.

Cryptorchidism represents a very common developmental aberration in human and animals. While in boys cryptorchidism is normally surgically corrected, in animals cryptorchidism typically leads to infertility. Cryptorchidism has a complex aetiology and can be caused by genetic as well as non-genetic factors. It was established that two genes encoding important signaling molecules play a key role in the control of the testicular descent from the abdominal cavity into the scrotum, which is mediated by the gubernacular ligament (Ivell and Hartung, 2003).

These signaling molecules are insulin-like factor 3 (INSL3) expressed by the Leydig cells of the fetal testis and its receptor expressed on the gubernaculum, which is called leucine-rich repeat-containing G protein-coupled receptor 8 (LGR8). Male knockout mice for either Insl3 or Lgr8 develop bilateral cryptorchidism (Gorlov *et al.* 2002). In a few human crytorchidism patients, mutations in the INSL3 or LGR8 genes have also been identified (Canto *et al.* 2003). No INSL3 or LGR8 mutations have so far been identified in cryptorchid stallions. Interestingly, however, it was demonstrated that in unilateral cryptorchid stallions, INSL3 expression is upregulated and LGR8 expression downregulated in the cryptorchid versus the descended testis (Klonisch *et al.* 2003).

Spermatogenesis

Early differentiation and meiosis

The spermatogonia derive from primordial germ cells and divide mitotically within the testis. Upon beginning differentiation, they become primary spermatocytes and enter meiosis. After the recombination of the parental chromosome and the first meiotic division, they form secondary spermatocytes. The secondary spermatocytes undergo the second meiotic division to become round spermatids. The process of spermatogenesis is dependent on two further cell types: Sertoli cells that are thought to function primarily as supporting and nourishing cells for the spermatogonia and the Leydig cells outside of the seminiferous tubuli that are responsible for testosterone secretion. Both cell types are involved in the complex endocrine and paracrine regulation of spermatogenesis.

From human medicine and the analysis of mouse mutants, many genetic aberrations are known that interfere with normal spermatogenesis and typically lead to azoospermia (Matzuk and Lamb, 2002; Liska, 2003). One of the earliest steps in spermatogenesis is the differentiation of primordial germ cells into spermatogonia. These cells are dependent on the expression of the c-kit proto-oncogene (KIT) and the KIT-ligand or stem cell factor gene (KITLG). Mouse mutants with defects in either gene exhibit male sterility due to drastically reduced numbers of primordial germ cells (Godin *et al*. 1991; Kissel *et al*. 2000).

Common human genetic aberrations leading to failure of spermatogenesis are microdeletions of the Y-chromosome. These microdeletions are frequently found in three azoospermia factor regions on Yq11, which are termed AZFa, AZBb, and AZFc (Krausz *et al*. 2003). The growing knowledge of the equine Y-chromosome allow molecular genetic analyses whether similar microdeletions are also a cause for infertility in horses (Raudsepp *et al*. 2004). The AZFc region in humans contains a cluster of Deleted in Azoospermia (DAZ) genes that seems to be primate-specific (Yen, 2004).

Meiosis represents an essential step during spermatogenesis. Consequently, mutations in genes that are required for meiosis often lead to non-obstructive azoospermia and infertility. One example of this group, again known from human medicine, is the synaptonemal complex protein 3 (SYCP3). Mutations in this gene cause meiotic arrest in the late pachytene stage and subsequent degeneration of the spermatocytes during the first meiotic division (Miyamoto *et al*. 2003). Male Sycp3 knockout mice were also sterile and confirmed the findings from human patients. Interestingly, the female Sycp3 knockout mice proved to be fertile, although their oocyte development was also impaired (Yuan *et al*. 2000; Yuan *et al*. 2002).

Spermiogenesis (post-meiotic sperm differentiation)

After the completion of meiosis, spermatids need to undergo further differentiation steps to become spermatozoa with their very specialized morphology. The round spermatids eventually elongate and differentiate into spermatozoa that are shed into the lumen of the seminiferous tubule. During their terminal differentiation, the histones of the spermatid chromosomes are replaced by protamines that ensure a very tight and robust packing of the DNA in the nucleus. Most of the cytoplasm is lost in a process called “cytoplasmic extrusion”. Specialized structures such as the flagellum and the acrosome at the sperm head are formed. Several gene mutations have been discovered that interfere with the spermiogenesis.

Gopc knockout mice are an animal model, where the correct acrosome formation is blocked. The Gopc protein is a Golgi associated protein with as yet unknown cellular function. However, male Gopc knockout mice, which are infertile, show globozoospermia, i.e. their sperm heads are round without acrosomes (Yao *et al*. 2002). Another gene involved in spermiogenesis that was identified during the analysis of knockout mice is the casein kinase II, alpha-2 subunit gene (Csnk2a2). Csnk2a2 knockout mice show oligozoospermia and globozoospermia with abnormally shaped sperm heads (Xu *et al*. 1999).

Sperm maturation

Spermatozoa that are produced in the testis are still immobile and not able to fertilize an oocyte. The immobile testicular spermatozoa have to undergo an additional process called sperm maturation, which is still only rudimentary understood. Sperm maturation brings about changes in membrane lipid composition and surface proteins. Only after sperm maturation, which begins during the passage through the epididymis and is subsequently promoted by different secretions from the accessory glands, spermatozoa acquire the ability to fertilize an egg. Soluble seminal plasma proteins that are produced by the epididymis and the accessory glands play an important role during this process. Some of these proteins bind to the surface of spermatozoa, where they might act as binding partners for surface structures in the female genital tract. Other seminal plasma proteins might be required for the modulation of the female immune system to suppress an adverse immune reaction directed against the spermatozoa. Initial results from human and cattle seem to confirm that specific sperm surface proteins can be used as markers for male fertility (Sullivan, 2004; Moura, 2005). Spermatogenesis and spermiogenesis are generally better conserved physiological processes across related species than sperm maturation. Haase *et al*. (2005). suggests that there are considerable species specific differences in the expression of seminal plasma proteins that contribute to sperm maturation.

A few examples of seminal plasma proteins that have been identified in the horse include the family of the cysteine-rich secretory proteins (CRISPs), the sperm adhesin family, and a protein family with variable number of fibronectin type II domains (Ekhlasi-Hundrieser *et al*. 2005). Within the CRISP family, three members have been described. However, their proposed functions are still mostly hypothetical. CRISP1 is primarily expressed in the epididymis and it was suggested that this protein attaches to the sperm surface, where it potentially plays a role during sperm-oocyte fusion (Cohen *et al*. 2000). CRISP2 is mainly expressed in testis, where it might mediate interactions between Sertoli cells and nascent spermatocytes (Maeda *et al*. 1999). CRISP3 in mouse and human is expressed in little amounts in the genital tract but also in the salivary gland, and some cell types of the immune system. These data imply a possible immune modulatory function for this protein (Udby *et al*. 2002). In contrast to all other investigated species, CRISP3 is expressed in huge amounts in the seminal plasma of stallions. In stallions, CRISP3 is expressed starting in the epididymis throughout the rest of the genital tract, with the highest expression in the ampulla (Schambony *et al.* 1998a, b). The high expression of CRISP3 suggests that this protein may have an important function in equine reproduction.

The genes for seminal plasma proteins consequently represent candidate genes for male fertility traits. As the different seminal plasma proteins apparently exhibit some functional redundancy, mutations in their genes could either cause infertility or rather quantitative changes in the fertilizing capacity of a fertile stallion. All three CRISP genes have been characterized in the horse and it was established that they do exhibit considerable variation between stallions (Giese *et al.* 2002a, b).

In other livestock species, quantitative variations in male fertility are also of great commercial interest. Especially semen quality traits could eventually play a role for the selection of male breeding animals used in artificial insemination stations (Robinson and Buhr, 2005). A recent study in pigs revealed initial clues that polymorphisms within ACTN1 and ACTG2 might be associated with different male reproductive performance traits (Wimmers *et al.* 2005). These genes encode alpha 1 actinin and gamma 2 actin, respectively. It was proposed that these proteins could be involved in membrane changes during the acrosome reaction.

Sperm motility

Upon ejaculation, spermatozoa must be able to fulfill several cellular functions including active movement inside the female genital tract, which are essential for successful fertilization. The CATSPER family of Ca2 + channels has been proven to be critical for normal sperm motility and male fertility. Because these proteins are transmembrane proteins, they offer particularly enticing targets as male contraceptives. On the other hand, their apparent role in flagellar function makes it likely that mutations in the CATSPER genes (sperm-specific pH-gated calcium channels) will affect male fertility. Male CatSper1 and CatSper2 knockout mice are sterile in association with severe aberrations of sperm motility (Ren *et al.* 2001; Quill *et al.* 2001; Quill *et al.* 2003). Mutations in the human CATSPER genes have been implicated as causes of infertility in men (Avidan *et al.* 2003; Nikpoor *et al.* 2004). The soluble adenylyl cyclase (SAC) is an important signaling molecule in sperm, which serves as bicarbonate sensor (Chen *et al.* 2000). Male Sac knockout mice are sterile in association with poorly motile spermatozoa (Esposito *et al.* 2004). Characterization of this cyclase is highly significant to our understanding of the signaling pathways that regulate mammalian sperm motility. Mammalian sperm motility is regulated by a cascade of cAMP-dependent protein phosphorylation events mediated by protein kinase A. The highly conserved A-kinase anchor protein 4 (AKAP4) has been shown to be involved in the compartmentalization of protein kinase A in the flagellum in several mammalian species. Interference with the protein kinase A/AKAP4 interaction results in immotile bovine sperm (Vijayaraghavan *et al.* 1997). Male Akap4 knockout mice are sterile in association with morphologically abnormal flagella/fibrous sheath formation (Miki *et al.* 2002). The equine AKAP4 gene has been partially cloned and characterized (Turner *et al.* 2005).

Flagellar function is dependent on the availability of sufficient ATP. The sperm specific isoform of glyceraldehyde-3-phosphate dehydrogenase (GAPDHS) has been proven to be critical in energy production in mature sperm. Male Gapdhs knockout mice are sterile in association with abnormal sperm motility and significantly reduced ATP production (Miki *et al.* 2004).

The cytochrome P450 aromatase (arom P450) could be used as marker of sperm quality, particularly in the acquisition of its motility. A higher ($P<0.01$) expression of aromP450 transcript was found in spermatozoa obtained from the good quality semen (higher mass motility) to that in spermatozoa of poor quality semen (low mass motility) (Tiwari *et al.* 2008).

Sperm quality

Selecting sires with consistently high semen quality is a major challenge in artificial insemination (AI) programs. Among prevailing sperm abnormalities, the sperm cytoplasmic droplet . Lovercamp *et al.* (2007) evaluated two candidate fertility marker proteins associated with sperm cytoplasmic droplet, including 15-lipoxygenase (15-LOX) and ubiquitin (UBI) and suggested that average litter size could be increased by selecting boars with lowest UBI and 15-LOX semen levels for AI service. The follicle-stimulating hormone (FSH) acts on the Sertoli cells in the seminiferous tubules of the testis and regulates spermatogenesis up to the secondary spermatocyte stage. Dai *et al.* (2009) used polymerase chain reaction single-strand conformation polymorphism (PCR-SSCP) and sequencing of the bovine FSH β-subunit gene (FSHB) to investigate the effect of FSHB on the quality of fresh and frozen semen in bulls.

They identified 13 substitutions and 1 insertion in the upstream regulation region and in the coding region of exon 3, which were all linked together. The mutations of the 5'-upstream regulation region altered the binding sites for transcription factors, and may result in alterations in the serum FSH concentrations. Bulls with this genotype exhibited lower semen quality, poor freeze resistance, and lower fertility.

Fertilization

Fertilization rate is heavily influenced by male factors. Even among bulls used commercially for artificial insemination that have passed routine fertility tests, a difference in conception rate exists. Abdel Dayem *et al.* (2009) suggest that the ability of sperm to bind the zona pellucida is related to fertility. Osteopontin (OPN) was identified as one of the fertility proteins expressed in the accessory sex gland fluid and associated with dairy bull fertility (Moura *et al.* 2006), OPN plays a role in sperm-binding and fertilization (Moura, 2005). Cluster-of-differentiation antigen 9 (CD9) gene expressed in the male germline stem cells is crucial for sperm-egg fusion, and was therefore selected as candidate gene for boar semen quality. It transcribes a key protein during sperm-egg fusion in mammals (Le Naour *et al.* 2000). The association of CD9 with boar sperm quality and fertility trait was analyzed by using mRNA and protein expression profiles (Kaewmala *et al.* 2011), they found that CD9 plays a crucial role during sperm development, especially within the epididymis where the maturation of the sperm, a key process for the sperm quality and motility takes place. Moreover, animals carrying alleles A were found to have higher sperm motility.

Hormone and hormone receptors

Hormone and hormone receptors are presumed to be good candidate genes for the reproductive traits because they modulate limiting steps in many reproductive pathways (Vincent *et al.* 1998). Candidate genes for many hormones were investigated by Lin *et al.* (2006) for their association with sperm quality traits. Analysis of variance revealed significant association of gonadotropin releasing hormone receptor with motility ($P=0.0161$), plasma droplets rate ($P=0.0048$) and abnormal sperm rate ($P=0.0201$), inhibin beta A was found to have significant effects on plasma droplets rate ($P=0.0318$) and abnormal sperm rate ($P=0.0067$), inhibin beta B was significant ($P=0.0360$) for sperm concentration trait. The hypothalamic gonadotropin-releasing hormone (GnRHR) is a key regulator of the reproductive system, triggering the synthesis and release of LH and FSH in the pituitary. The gonadotropin-releasing hormone receptor is a guanine nucleotide-binding protein-coupled receptor with a characteristic seven transmembrane domain motif. It transduces the hypothalamic message carried by the decapeptide gonadotropin-releasing hormone. At the gonadotrope cell surface the hormone binds to the receptor, leading to pituitary synthesis and secretion of gonadotropins (Cohen, 2000). GnRHR deficiencies and GnRHR mutations are associated with idiopathic hypogonadotropic hypogonadism or Kallmann's syndrome in humans (Seminara *et al.* 1998; Bo-Abbas *et al.* 2003), because GnRHR mutations reduce GnRHR binding and/or activation of inositol triphosphate or phospholipase C (Achermann and Jameson, 1999).

Prolactin receptor (PRLR) mRNA expression is almost consistent with PRL binding sites except for elongated spermatids and spermatozoa suggesting that PRL may have direct effects on spermatogenic cells (Hondo *et al.* 1995). PRLR knockout mice showed delayed fertility in males; the effects of PRL on testosterone production of Leydig cells and accessory reproductive glands can obviously be finally compensated by other regulatory factors (Bole-Feysot *et al.* 1998). Seminal plasma prolactin concentrations in man were related directly to sperm concentrations and motilities (Aiman *et al.* 1998).

Follicle stimulating hormone (FSH) acts on the germinal cells in the seminiferous tubules of the testis and is responsible for spermatogenesis up to the secondary spermatocyte stage; later androgens from the testis support the final stages of spermatogenesis (Hafez and Hafez, 2000). FSH influences the sexual behaviour and testicular morphology and function of the boar (Zanella *et al.* 1999). FSH is a heterodimer composed of alpha and beta subunits that are coded by two distinct genes. The beta subunit offers specificity. The expression of FSHB gene in boar is positively associated with activin beta B-subunit (Li *et al.* 1998a). Male homozygous FSHB knockout mice had normal levels of serum testosterone but had small testes and oligospermia (Layman, 2000).

Luteinizing hormone (LH) influences the sexual behavior and testicular function of the boar (Ellendorff *et al.* 1970). The interstitial cells (Leydig cells) produce androgens after LH stimulation (Hafez and Hafez, 2000). LH is a glycoprotein composed of an alpha and a beta subunit with a molecular weight of 30000Da and a biologic half life of 30 min. LHB gene expressed during spermatogenesis and male sexual behavior and FSHB may participate in spermatogenesis, whereas LHB is more involved in spermatogenesis (Degani *et al.* 2003). A mutation causing inactivation of the LH beta subunit in human leads to absence of Leydig cells, resulting in a lack of spontaneous puberty and infertility (Huhtaniemi *et al.* 1999).

Follistatin (FST) is a protein isolated in testis that may modulate a range of testicular actions of activin (Meinhardt *et al.* 1998). It is not only inhibits the secretion of FSH similar to that of inhibins (INHs) but also binds activin (ACN) and neutralies its biological activity, thus it modulates the secretion of FSH. The gonads are the main source of INH and related proteins, which contribute to the endocrine regulation of the reproductive system. Sertoli cells in the male produce INHs. In male, INHs are secreted via the lymph. By inhibiting FSH release without altering LH release, INHs may partly be responsible for the differential release of LH and FSH from the pituitary. Besides the regulation of pituitary FSH, INHs related proteins regulated Leydig cell function (Risbridger *et al.* 1996) over expression of inhibin alpha-subunit gene leads to a disruption of the normal INH-to-ACN ratio and to reproductive deficiencies, therefore INH and ACN act to regulate FSH secretion and are essential for normal gonadal function (Cho *et al.* 2001). The expression of INHBA and INHBB, FST and ACNA receptor messenger RNA (mRNAs) in different stages of seminiferous epithelial cycle regulated spermatogenesis (Kaipia *et al.* 1992). Both levels of serum INHB and seminal plasma INHB could reflect testis spermatogenesis status. Levels of seminal plasma INHB could also reflect the function of seminiferous duct (Hu and Huang, 2002).

Molecular markers for female fertility

Regulation of ovarian function

Follicle stimulating hormone (FSH) plays a central role in regulation of ovarian function in mammals. The actions of follicle stimulating hormone are mediated through receptors present on the granulosa cells of the ovary. The first isolation and characterization of FSHR cDNA from buffalo ovary was by Minj *et al.* (2008). Sequence analysis indicated that the buffalo FSHR cDNA sequence comprised of an open reading frame of 2085 bp encoding a 695 amino acid protein. Its nucleotide sequence showed more than 80% similarity to the homologous genes of mammalian species. At amino acid level buffalo FSHR exhibited a high percentage (84-96.7%) of identity with the corresponding mammalian homologs (Minj *et al.* 2008).

The study done by Monget and Bondy (2000) illustrated that the free IGF-I increases the granulosa cells sensitivity to follicle stimulating hormone in the ovary. Therefore, IGF-I is important in the process of follicular development and ovulation in cattle. IGF-IR expression can be detected in almost all tissue and cell types during embryogenesis, suggesting the importance of IGF-I in early development (Bishop *et al.* 1989). The IGF-IR is abundantly expressed in ovary, uterus and the embryo, with significant reduction in expression levels at adult stages. IGF-IR showed inhibitory effects of cortisol in ovarian function during stress (Spicer and Chamberlain, 1998).

In addition to the well established regulatory role of pituitary gonadotropins and growth factors in regulating the development and function of antral follicles, cocaine-and amphetamine-regulated transcript (CART) is potentially associated with follicle health status. CART is a specific inhibitor of basal estradiol production by bovine granulosal cells, but the effects are dependent on the stage of granulosa cell differentiation, suggesting a potential key role for CART in regulation of follicular atresia (Kobayashi *et al.* 2004).

Folliculogenesis, oogenesis and ovulation

The mammalian oocyte regulates folliculogenesis, ovulation, fertilization, and early embryogenesis by producing factors that have key functions in these developmental processes (Hamatani *et al.* 2004; Sirard *et al.* 2006). Among the known factors produced by the oocyte are growth differentiation factor-9 (GDF-9) and bone morphogenetic protein-15 (BMP-15), which control both proliferation and gene expression in granulosa cells (Hsueh *et al.* 2000). Other oocyte-specific factors such as maternal antigen that embryos require (Mater) and zygote arrest 1 (Zar1) are required for early embryonic development through the maternal embryonic transition (Wu *et al.* 2003). Furthermore, Hamatani *et al.* (2004) identified 134 oocyte-specific genes with changes in expression level associated with maternal embryonic transition in the mouse, suggesting a greater need for research to investigate the influence of oocyte quality and oocyte-specific genes on folliculogenesis and early embryonic development.

Period 1 (Per1), a clock gene involved in circadian rhythms, was localized to the oocyte in the mouse ovary but its function was not determined (Johnson *et al.* 2002). Because Hamatani *et al.* (2004) did not identify Per1 in their global study of genes differentially expressed during early embryogenesis; Per1 is more likely to be involved in folliculogenesis and oogenesis than to be involved in early embryonic development. Per1 mapped to a region of mouse chromosome 11 that is syntenic to bovine chromosome 19, where there is a putative quantitative trait loci (QTL) for ovulation rate (Kirkpatrick *et al.* 2000). Per1 mRNA was localized to the ruminant oocyte in secondary and antral bovine follicles (Cushman *et al.* 2007).

Studies of gene expression in cumulus cells not only will advance our understanding of the regulation of oocyte growth and maturation, but also may yield molecular markers for the developmental potential of their enclosed oocyte because any abnormal patterns of gene expression in cumulus cells could be either causes or consequences of abnormal development of the oocyte (Zhang *et al.* 2005). The oocyte is also an important modulator of granulosa/cumulus cell function. In the mouse, cumulus expansion around the time of ovulation will not occur in the absence of the oocyte (Salustri *et al.* 1990). Growth and differentiation factor 9 (GDF-9) mediates this oocyte effect on cumulus expansion (Elvin *et al.* 1999).

In addition, GDF-9, as well as bone morphorgenic protein-15 from oocytes, mediates other regulatory effects of the oocyte on granulosa/cumulus cells (Yan *et al.* 2001).

For example, GDF-9 inhibits FSH-induced steroidogenesis and LH receptor expression and up-regulates prostaglandin-endoperoxide synthase-2 (COX-2) and the type 2 receptor for prostaglandins in cumulus cells of preovulatory mouse follicles (Elvin *et al.* 1999; Varani *et al.* 2002). Other genes under oocyte GDF-9 regulation include urokinase-type plasminogen activator (uPA) and pentraxin-3 (Ptx3). A 36-fold increase in Ptx3 expression was induced by GDF-9 in mouse cumulus cells, and inactivation of Ptx3 in the mouse disrupted cumulus oophorus formation around the oocyte and reduces oocyte fertilization rate (Varani *et al.* 2002). Survivin is a 16.5-kDa, an inhibitor of apoptotic protein; it is thought to protect the embryos from apoptosis by inhibiting an apoptotic pathway involving caspase activity (Kawamura *et al.* 2003). The expression of survivin was related to the quality of cumulus-oocyte complexes (COCS), their developmental competence and the quality of in vitro produced blastocysts. Consequently, survivin may be a good candidate marker for embryo quality (Jeon *et al.* 2008) as it was significantly higher ($P<0.05$) in good compared to poor quality COCS. Tremblay *et al.* (2006) have identified the bovine oocyte-secreted protein 1 gene as being one of the few known oocyte-specific markers. The expression profiling using real-time PCR revealed that mRNA levels were high in germinal vesicle (GV) stage oocytes and gradually decreased until the blastocyst stage, at which time they were undetectable. Yang *et al.* (2010) studied the polymorphisms in the 5' upstream region of the FSH receptor gene using SSCP analysis and their association with superovulation traits in Chinese Holstein cows.

They detected three genotypes CC, CD and DD. Cows with CC genotype had a significant increase in the total number of ova. Follicle-stimulating hormone β (FSHB) was chosen as a candidate gene because it functions in the maturation of small and medium follicles into large follicles that ovulate (Mannaertz *et al.* 1994). In a candidate gene analysis, Li *et al.* (1998b) found additive effects on litter size associated with a marker within FSHB.

The oestrogen receptor (ESR) gene has been identified as a major gene for litter size in Meishan and Large White pig breeds. Omelka *et al.* (2005) reported the possibility of ESR utilization in marker-assisted selection to increase litter size only in Landrace pigs.

Puberty and estrous cycle

Puberty is the final stage of maturation of the hypothalamic pituitary-gonadal axis, culminating in an adult phenotype, and is marked by changes in circulating gonadotropins and increased levels of sex steroids (Wu *et al.* 1996). The gonadotropin-releasing hormone (GnRH) induced secretion of the gonadotropic hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary is essential to invoke puberty and maintain reproductive function.

The G protein-coupled receptor GPR54 (Lee *et al.* 1999) is a key protein involved in the pubertal activation of the hypothalamic pituitary gonadal axis because mice and humans with mutations in this receptor are sterile with hypogonadotropic hypogonadism (De Roux *et al.* 2003; Semple *et al.* 2005). A series of overlapping peptide ligands (kisspeptins) for the GPR54 receptor are produced by the Kiss1 gene (Muir *et al.* 2001; Ohtaki *et al.* 2001).

Genetic disruption of steroid receptor coactivator-3 (SRC-3) in mice results in a pleiotropic phenotype showing dwarfism, delayed puberty, reduced female reproductive function, and blunted mammary gland development. Hormonal analysis indicates that SRC-3 plays a role in both the growth hormone regulatory pathway and the production of estrogen (Xu *et al.* 2000).

Steriodgenic acute regulatory (STAR) protein is an important factor in the acute regulation of steroidogenesis. In mammalian ovary, STAR protein mediates the true rate-limiting step of transport of cholesterol from outer to inner mitochondrial membrane. Differential expression of STAR messages was observed during estrous cycle in buffalo ovary and synergistic action of IGF-I on FSH stimulation of STAR gene (Malhotra *et al.* 2007).

Pregnancy and prenatal mortality

The bovine placenta secretes multiple molecules during implantation and placentation, many of which are produced by binucleate cells. Production of prolactin-related protein 1 (PRP-1), a member of the non-classical prolactin-related family, was investigated during the implantation period in cows. Yamada, *et al.* (2002) found that bPRP-1 may play a role before implantation and that bPRP-1 may be an excellent marker for trophoblastic cell differentiation, as well as a candidate for pregnancy diagnosis. Abnormalities in developmental processes during embryogenesis including trophoblastic elongation and blastocyst implantation can be attributed to prenatal mortality (Spotter and Distl, 2006). Cathepsins are lysosomal cysteine proteases that have been implicated as modulators of invasive implantation in cats (Li *et al.* 1992). Cathepsin L (CTSL) activity in the pig uterus increases at the time of trophoblast elongation with peak activity on day 15 of pregnancy (Geisert *et al.* 1997). The high affnity of CTSL for collagen (Kirschke *et al.* 1982) and elastin (Mason *et al.* 1982) suggests that it may play a role in placental attachment on days 13–18 of gestation through limited proteolysis of the uterine epithelial glycocalyx (Geisert and Yelich, 1997).

Inter-α trypsin inhibitor heavy chain 4 (ITIH4) is a glycoprotein that may play a role in conceptus-uterine interactions for the establishment of pregnancy in pigs, probably as an acute phase protein for protection of the uterus from the inflammatory response induced by conceptus attachment to the uterine epithelium (Geisert *et al.* 1998). Endometrial gene expression of ITIH4 in pig was detected during estrous cycle (days 0-18) and early pregnancy (days 10-18).

The effects of leukemia inhibitory factor (LIF) in many physiological systems include proliferation, differentiation, and cell survival (Hilton, 1992; Metcalf, 1992). These biological effects of LIF are mediated by binding to a specific LIF receptor subunit (LIFR) (Gearing *et al.* 1991). The essential role of endometrial synthesized LIF in blastocyst growth and implantation in mice (Stewart, 1994; Savatier *et al.* 1996) implies that the LIF/LIFR system may also serve a vital function in conceptus development and implantation in pigs (Geisert and Yelich, 1997). This implication is supported by the detection of LIF gene expression in porcine endometrium at the time of blastocyst attachment and the presence of LIFR mRNA in porcine periimplantation conceptuses (Modric *et al.* 2000).

The cellular effects of epidermal growth factor (EGF) and EGF-like proteins, including transforming growth factor α (TGFα), heparin-binding EGF, and amphiregulin, are mediated through binding to the membrane-bound EGF receptor (EGFR) (Prigent and Lemoine, 1992). All of these ligands are expressed by the pig endometrium during early pregnancy (Kennedy *et al.* 1994; Kim *et al.* 1995).

Uterine serpins (SERPINA14) play important roles during pregnancy in the farm animals. Uterine serpins (SERPINA14, previously named as UTMP), member of a large serpin super family of serine protease inhibitors (Ing and Roberts, 1989), are secreted from the uterine endometrium mainly under the influence of progesterone (Moffatt *et al.* 1987). Kandasamy *et al.* (2010) cloned and characterized cDNA sequence encoding the bubaline SERPINA14. They also studied its spatio-temporal expression in the uterine endometrium during early pregnancy (Days ~30 of gestation) the level of SERPINA14 mRNA was as high as that during stage II of the estrous cycle. The SERPINA14 mRNA was localized in the glandular epithelium. The differential spatio-temporal expression of SERPINA14 in the uterine endometrium of buffalo suggests its plausible important roles in reproduction.

The osteopontin (OPN) gene has been implicated in transport and buffering of Ca2 + from the maternal circulation to the conceptus; this is supported by evidence of expression of the gene in cells of mouse placenta and (Waterhouse *et al.* 1992). The existence of binding sites for estrogen and glucocorticoids within the promoter of the OPN gene in mice (Craig and Denhardt, 1991) argues for a regulation of its transcription by steroid hormones known to be involved in reproduction.

Marson *et al.* (2008) studied the effects of Alu I polymorphism of FSHR gene (exon 10) on sexual precocity in European-Zebu composite beef heifers from six different breeds. Three genotypes were detected (GG, CG and CC) with higher frequency of heterozygote in all tested breeds. The heterozygous heifers showed a higher pregnancy rate, but no significant effects were observed on the probability of pregnancy.

Amphiregulin (AREG), a member of the epidermal growth factor family, is one of the genes important for appropriate embryonic attachment (Giudice, 1999). Uterine IGF-I expression was detected during the estrous cycle and early pregnancy, indicating that its expression plays a role in embryonic development and uterine function (Watson *et al.* 1999; Robinson *et al.* 2000).

The single transducers and activators (STAT) proteins are known to play an important role in cytokine signaling pathways. They act as signal transducers in the cytoplasm and transcription activators in the nucleus. Single Transducers and Activators of Transcription 5 B (STAT5B) was a crucial signaling protein mediating the biological effects of growth hormone, while the key function of STAT5A was to transduce the signals initiated by prolactin receptors (Tan and Nevalainen, 2008). STAT5A is a member of the interferon-ô and placental lactogen signaling pathway. Genes of this pathway are involved in initiation of pregnancy, milk production and health traits. It is involved in signal transduction within a variety of cells, including the uterus and mammary epithelial cells (Brym *et al.* 2004; Khatib *et al.* 2008).

Many studies have shown that STAT5A is expressed in oocytes at the metaphase II stage (before fertilization) and in 2-cell, 4-cell, morula, and blastocyst stages (Rodig *et al.* 1998) which suggests a possible role of this gene in fertilization and early embryonic development (Akira, 1999).

Expression analysis revealed that STAT5A in cattle is primarily monoalle1ically expressed in early embryonic stages but biallelically expressed in later fetal stages (Khatib *et al.* 2009).

Its roles in embryonic development and in the signal transduction pathway of interferon-tau make it has a key role in the initiation and maintenance of pregnancy in ruminants. Deficiencies in both STAT5A and STAT5B were recorded by Pickorz *et al.* (2004) as loss of pregnancy during mid-gestation and increase in ovarian 20-hydroxysteroid dehydrogenase (20-HSD) and decrease in serum progesterone, which normally declines only immediately before parturition.

Quantitative Trait Locus (QTL) of female fertility located on *Bos taurus* chromosome 3 (BTA3), QTL-F-Fert-BTA3 affecting female fertility was studied by Coyral-Castel *et al.* (2010), Ovarian follicular dynamic and fertility parameters were compared between homozygous females carrying the favourable haplotype "fertile+"or the unfavourable haplotype "fertile-". They found that pregnancy rate of "fertile+" was higher than in "fertile-" primiparous cows, at 35 d after the AI. Leptin, the hormone encoded by obesity (Ob) gene, is a 146 aa protein with a tertiary structure similar to cytokines (Zhang *et al.* 1994). Using reverse transcription and polymerase chain reaction analysis, Sayed-Ahmed *et al.* (2003) demonstrate that leptin is expressed both in the adipose tissue and in the lactating mammary gland tissue of Egyptian water buffalo.

Parturition

Oxytocin gene transcription in supraoptic nucleus neurons is rapidly increased during parturition and remains high in lactation, times when oxytocin neurons show their strongest physiological secretory activity. Thus, oxytocin gene expression may be regulated by mechanisms closely linked to excitation of the neurons (Douglas *et al.* 1998). FosB expression is co-involved with Fos in the neural activation during parturition and lactation in rats (Lin *et al.* 1998). It has also been shown that the oxytocin receptor gene contains an AP-1 site within its promoter (Rozen *et al.* 1995), thus, one of the possibilities is that FosB and Fos activate the transcription of the oxytocin receptor in these regions during parturition and lactation. The lowest gene transcription profiles of prostaglandin E synthase (PGE2) and enzymes involved in its synthesis (cyclooxygenase-2; COX-2) was also coincidental with the surge in cortisol concentrations, indicating that this hormone plays a main immunomodulatory role around parturition (Silva *et al.* 2008).

Post partum period

Anestrum

The most common cause of infertility in buffaloes is anestrum. During late maturity the ovaries are in a state of true anestrum. One of the predominant causes of true anestrum is a low level of ovarian estrogens. The key enzyme in estrogen biosynthesis is cytochrome P450 aromatase, encoded by CYP19 gene. CYP19 gene polymorphism was analyzed by single strand conformational polymorphism in buffaloes of different fertility performance (Kumar *et al.* 2009). Moreover, RT-PCR analysis showed that the CYP19 gene expression was significantly ($P<0.05$) higher in granulosa cells of large follicles as compared to the other tissues (Sharma *et al.* 2009).

Calving interval

Calving interval is the period between consecutive calving. Among the reproduction traits calving interval is the most important criterion (Singh *et al.* 2000). The losses due to prolonged calving intervals are, loss of milk, excessive additional feed coast, delayed in replacement stock, disinterest of farmer in open and dry buffalo resulting in further deterioration of animals and culling of potentially productive animals (Shah, 2007). This implies that the success of buffalo production depends on the ability to control calving intervals.

The candidate genes investigated by Mostafa (2011) in Egyptian buffaloes were follicle-stimulating hormone receptor (FSHR), insulin-like growth factor-I (IGF-I), insulin-like growth factor-I receptor (IGF-IR), inhibin beta A (INHBA) and signal transducers and activators of transcription 5A (STAT5A).

These genes were studied in high and low fertility buffaloes according to the calving interval (CI). The correlations were found between FSHR, IGF-IR and STAT5A genes with CI while IGF-I and INHBA gene loci had no impact on CI. Insulin-like growth factor-I receptor (IGF-IR) mRNA was detected in granulosa cells and was localized to follicle granulosa cells, confirming earlier observations in the cow (Perks *et al.* 1999).

Schoenau *et al.* (2005) studied the association between single-strand conformation polymorphism in a fragment of 335-pb of IGF-IR and productive and reproductive traits in Holstein females.

The population genotype frequencies were 82.1% and 17.9%, for AA and AB genotypes, respectively. They reported no association between the identified polymorphism and the age at first calving, calving interval and milk yield. The lactation length was positively associated with the absence of B allele. Animals carrying the AA genotype presented a longer lactation period.

CONCLUSION

Fertility is a lowly heritable trait and therefore, it is difficult to improve through traditional phenotypic selection. The presence of a DNA marker may enable the rate of genetic improvement in fertility to be greatly increased.

Presently, the pace of development of molecular markers is tremendous, and the trend suggests that explosion in marker development will continue in the near future. It is expected that molecular markers will serve as a potential tool to geneticists and breeders to evaluate the existing germplasm, and to manipulate it to create animals as desired and needed by the society.

The use of DNA markers combined with reproductive advancements such as prepubertal oocyte and sperm recovery, in vitro maturation, in vitro fertilization, intracytoplasmic sperm injection, and propagation of embryonic stem cells offer the promise of tremendous genetic improvment through increased intensity and accuracy of selection and reduction in the generation interval.

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