FUTURE REPRODUCTION IN BEEF CATTLE

George E. Seidel, Jr.
Animal Reproduction and Biotechnology Laboratory
Colorado State University
Fort Collins, CO 80526-1683

Introduction

There are many ways of organizing thinking about future reproduction in beef cattle. I will use two broad categories: 1.) routine practices such as AI with synchronization of ovulation, potentially applicable for over 90% of cattle and 2.) specialized practices such as cloning, usually appropriate for less than 10% of cattle. With time and refinement, the latter category often evolves into the former. Also, seedstock producers will justifiably be using the more specialized procedures to a greater extent than commercial producers. This makes sense since any genetic gains get spread over the commercial sector, so costs of new approaches, as reflected in seedstock prices, also get spread across more cattle than if limited to individual herds.

One additional issue is how far into the future should one speculate? The average generation interval in beef cattle is around 5 years, so breeding decisions, which female is mated to which male, will affect not only the resulting calf at birth, but also her performance as a calving 2-year-old nearly 3 years later, and as a mature cow 5 to 15 years later. Because some cattle die or are culled at various stages, for example due to not becoming pregnant, poor performance, injury, etc., an average animal in the herd is a result of a mating made over 5 years previously. Thus, on average, the benefits of a mating decision will occur about 5 years into the future, and importantly, the mating decisions made 5 years later will result in benefits, on average, 5 years after that. All this means that a time horizon of 10 years into the future is only two generation intervals and two mating decisions away.

Of course, mating decisions usually are made annually, and the herd improves incrementally with those decisions. The discussion, thus far, has concentrated on genetic aspects of cattle breeding. Even more important are the non-genetic aspects, such as simply getting heifers and cows pregnant economically. If no calf is produced, the genetic decisions are irrelevant. Thus, the first priority is to establish a pregnancy that will result in a saleable product; improved genetics is a secondary consideration.

The Basics

In cattle breeding over the next decade, we are stuck with some basic facts and realities. One of these is the seasonal availability of grazing, which fits perfectly with a 9+ months' gestation, post-partum anestrus, etc., when everything works as it should. However, with mismanagement, such as inadequate nutrition, low pregnancy rates for any reason, etc., animals will be pregnant out of synchrony with availability of feed. Thus, the first basic rule is to have good management, and this will be true forever. We already have reproductive tools, such as inducing puberty and shortening post-partum anestrus with progestins, to compensate for problems leading to delayed pregnancy.

One new tool might be selecting for shorter gestations. For example, it should be relatively easy to select for 5 to 7 days shorter gestation without compromising viability to any extent; moreover, calves would be slightly smaller, decreasing dystocia. Maybe decreasing the variability in gestation length would be even better – it is those slightly prolonged gestations with larger calves that often cause problems. We already have a tool for this, induced parturition with glucocorticoids, but this can be improved; inducing parturition often is problematic unless there is a known breeding date; otherwise, premature calves can result.

We also are constrained by biology, such as 3-week reproductive cycles, non-responsiveness to drugs at times, e.g. prostaglandin F-2∂ when there is no corpus luteum, and with heifers, GnRH when there is a corpus luteum. Compliance with protocols is essential, and a good foundation of nutrition and disease control including appropriate vaccinations is required to optimize reproduction; these will not change in the future.

Another basic fact is that under most circumstances, cross-breeding is more productive than straight breeding. We do not yet really understand the basic mechanisms of hybrid vigor, but benefits for traits like reproduction and longevity are substantial. Failing to use cross-breeding means giving up these benefits for the foreseeable future. A better understanding of hybrid vigor plus genomic technology may eventually enable having the advantages of hybrid vigor with straight breeding.

Routine Practices

What might we do differently in the future with the most powerful reproductive tool for beef cattle – artificial insemination with genetically superior semen, usually after synchronization of ovulation? What discourages use of AI is the necessity of processing cattle multiple times, typically three or four trips through the chute. One trip is obviously for AI, often coinciding with a GnRH injection. There is one recommended program for heifers that requires only a single additional processing event in the chute, which is feeding MGA for 14 days followed by a prostaglandin injection 19 days later, about 3 days prior to AI + GnRH. This fits well if one is feeding daily anyway, and the MGA can be formulated into range cubes to be fed on pasture. This approach, however, does not fit most production systems without greatly increasing labor and other costs.

One innovation that would permit handling cattle only twice is a subcutaneous device that dispenses hormones over a period of time. This device might be programmed to deliver GnRH, progesterone for a week, and then prostaglandin; it could be removed at the time of AI, or better yet be biodegradable with time.

A solution to another standard breeding problem, females that did not become pregnant to first service AI, is resynchronization. Currently, most of these are turned out with a clean-up bull and eventually become pregnant, or sometimes they are observed for estrus and rebred AI. These animals often do not calve within the desired 45-day window, thus tying up facilities and increasing labor costs, etc. Possibly we should consider resynchronization protocols like those developed for dairy cattle.

Use of selection based on genomics has resulted in intense pressure to reduce the generation interval in dairy cattle on the male side; similar measures also could be applied with beef cattle. Making males obviously requires females; inducing early puberty in both sexes is one approach to decreasing the generation interval. While this application will only apply to a few percent of cattle at most, related research may be applicable on a broader scale to produce heifers that are more fertile and cows with shortened post-partum anestrus.

Sexed semen is another tool that increasingly will be incorporated into AI programs. Pregnancy rates with sexed semen will probably continue to improve, possibly dramatically. Sperm are sorted one at a time, so there is an opportunity to discard defective ones. Currently, dead sperm already are discarded during sexing, but other criteria might be used such that the sperm in a sexed semen dose would be of higher quality and result in higher fertility than non-sexed sperm.

For nearly every mating, the offspring of one sex is of more value than the other sex. Therefore, if fertility is not compromised, and the extra cost for sexed semen is low, sexed semen will be used for most AI. Even for terminal cross situations, male calves at weaning are worth around $75 more than female calves due to higher weights and a higher price per pound received, partly because steers gain weight more efficiently than heifers.

Specialized Practices and More Futuristic Technology

I will provide my interpretation of the future potential for three futuristic technologies. All of these technologies are important for research, and most already have niche applications. Sometimes there is a tendency to "oversell" the value of technologies; on the other hand, it is wise to at least consider possible uses. In many cases, niche applications lead to refinements and improvements that make technologies more widely applicable.

In vitro fertilization and closely related technologies

Bovine in vitro fertilization procedures usually begin with in vitro oocyte maturation, but increasingly with in vivo oocyte maturation. The former is practiced when oocytes originate from immature follicles, aspirated transvaginally or from ovaries of slaughtered animals. In vitro oocyte maturation requires culturing the oocytes and associated cumulus cells for 20-24 hours in special media under special conditions. For in vivo oocyte maturation, females are given FSH and other hormones much as is done for routine superovulation, and oocytes are aspirated transvaginally around 24 hours after an LH surge, about 5-6 hours before expected ovulation.

The next step is to capacitate the sperm to be used. Capacitation is required for sperm to be capable of fertilization and involves removal of seminal plasma and semen extender from the sperm, treatment with heparin, and culture in medium with key ingredients including serum albumin.

The subsequent actual in vitro fertilization, is rather trivial, combining capacitated sperm and matured oocytes in the same fluid. Completion of capacitation usually occurs at this step.

After 6 to 20 hours of coincubation of sperm and oocytes, the oocytes (now fertilized 1-cell embryos) are removed from the sperm, and cultured for about 6 days in fluids that mimic those found in the oviduct. At this point, embryos that have developed normally can be frozen, or transferred fresh nonsurgically.

I have provided some detail about in vitro fertilization procedures to convey the complexity of the process. It requires a lot of record keeping since oocytes and semen come from a variety of donors and bulls. One other important point is that pregnancy rates with in vitro-produced embryos still are 10-25% lower than with embryos produced with routine superovulation and embryo transfer, especially if the embryos are frozen. However, these procedures are constantly improving, with greater success than a few years ago.

A major application of in vitro fertilization in the US is to combine the technology with sexing semen. Sexing sperm almost always is done with fresh semen, which then is frozen. What does not work satisfactorily with cattle is to freeze semen, then sex it, and then refreeze it. However, frozen semen that is sexed just prior to use for in vitro fertilization works well. Thus, most bulls with frozen semen, even those that are long dead, can be used to provide sexed embryos with this procedure. Note that very few sexed sperm are needed for successful in vitro fertilization since the sperm are mixed with oocytes in a very small volume of fluid. In some cases, particularly with people and horses, this concept is taken a step further and one sperm is injected into each oocyte (intracytoplasmic sperm injection). The sperm do not even need to be alive for this. Incidentally, the method can be used to salvage sperm if liquid nitrogen tanks fail, as long as the sperm did not get too warm for too long. Unfortunately, this process is expensive and has not been used very successfully in cattle.

In addition to the application with sexed semen just mentioned, in vitro fertilization fits several other situations. An obvious one is to circumvent some forms of infertility, which is the main application with humans. Genetically valuable cows sometimes become infertile due to disease, injury, or age so that the sperm and oocytes do not get together successfully in vivo, or the diseased reproductive tract becomes hostile to sperm, oocytes, or developing embryos. Circumventing such infertility, or even death of a donor cow, represents only an infrequent application in cattle. A more common application is that on average it is possible to get more calves per cow per unit time with in vitro fertilization than with routine embryo transfer. On average, only one or two pregnancies are achieved per donor per in vitro fertilization attempt, but this can be repeated frequently, even weekly with some protocols. It also is possible to obtain oocytes from cows pregnant up to 100 days of gestation by transvaginal procedures, without aborting the pregnancy.

There are two major problems with application of in vitro fertilization in cattle. First, procedures require complex logistics including precise timing both on the farm and in the laboratory, which usually is distant from the farm. Overnight shipments by air using portable incubators often are required. Attention to detail is needed for most reproductive technologies, but with in vitro fertilization, there are just more details requiring more precision in timing.

Second, the cost per pregnancy usually is considerably higher than, for example, with routine embryo transfer. Not only are there more costs on the farm, the in vitro fertilization services also are expensive, and all this is exacerbated by lower pregnancy rates, higher abortion rates, and slightly increased problems at calving. These increased costs are justified economically if the resulting calves are sufficiently valuable.

There are situations in which bovine in vitro fertilization is practiced under very different conditions than we have in the United States. The most impressive application is in Brazil, where hundreds of thousands of in vitro-produced embryos are transferred using Bos indicus breeds of cows. Those breeds produce about twice the number of oocytes per session as Bos taurus cows. Also, labor is cheap and more importantly, recipient costs are relatively low so that 35-40% pregnancy rates are quite acceptable. Use of these procedures in parts of Canada for dairy cows represents another niche for the technology, especially when combined with sexed semen. Much higher milk prices in Canada than the United States help to make this technology fit. It also will be increasingly appropriate for beef cattle breeding in the US as procedures become both more simplified and successful, and delivery systems improve.

Cloning by nuclear transfer

There are several methods of cloning but I will concentrate on nuclear transfer. This technology has many of the same components as in vitro fertilization, including requiring oocyte maturation and in vitro culture of resulting embryos. Fundamentally, the somatic cell nucleus replaces sperm in the process, so “fertilization” is always done microsurgically. There is the additional step of removing the native genetic material from the oocyte.

Costs per cloned calf produced are very high currently because costs of the procedures are substantive, pregnancy rates are low, abortion rates are high, and abnormalities in resulting calves are frequent. Usually intensive care at birth allows the calf to recover from these defects which are primarily effects of placental abnormalities. Despite the increased problems around the time of birth, once calves are stabilized, by a few days after birth most are normal for practical purposes.

Within the past few years, success rates with cloning procedures have increased, and costs, abortion rates, and abnormalities at birth have decreased. These trends will continue, making cloning useful for many more applications in beef cattle in the future.

Despite the costs, cloning cattle is profitable in a number of situations. An obvious application is for insurance purposes with valuable bulls. The sperm produced by a clone will be essentially identical genetically to sperm of the original, so it makes sense to have a younger genetic copy. Other current applications include cloning show winners, particularly club calves, and also valuable rodeo stock. Clearly, any cattle of sufficient genetic value to compensate for costs are appropriate for cloning, and cloning will fit more situations in the future.

A very important point is that cloning makes a genetic copy, not a phenotypic copy. Phenotypes are determined by genetics, environment, and epigenetic components, which I will not explain here. The environmental components are obvious, and right off include the uterus; since cloning requires embryo transfer, it is impossible to have the exact uterus, birth process, colostrum, etc. as occurred with the original dam. Growth conditions, exposure to environmental pathogens, etc. also will differ. For these reasons, cloning a phenotypically desirable animal often will lead to disappointment. An analogy with horses helps to explain this: cloning race winners usually will not result in race winners due to all the chance environmental components that result in race winners. However, cloning a stallion that on average sires race winners will result in a stallion that sires race winners.

One other option is to clone a steer to make a bull. This occasionally will make sense, but one clearly is copying because of a phenotype, and the resulting animal could be better, similar, or most likely, less desirable than the original.

A final point is that the US Food and Drug Administration has determined that cloned animals and their products, such as milk, are safe to eat. However, to date, cloned cattle usually are not slaughtered for human consumption so as to avoid adverse publicity for the cattle industry. Offspring of cloned animals are not considered problematic in this respect. The issue of eating cloned animals is likely to fade away in the future, but currently is still susceptible to sensationalization.

Transgenics

The third futuristic technology that I will consider is transgenics. A transgenic animal is defined as one that has a deliberately altered genetic make-up; usually the genetic change will be transmitted to future generations. The term transgenic has been replaced with “genetically modified organisms” in the popular press, especially as applied to plants. Nearly 90% of corn and soybeans grown in the United States is transgenic. The safety of transgenic organisms for food is determined by the Food and Drug Administration on a case-by-case basis. The only transgenic animal approved as safe so far is salmon with genetically modified growth hormone.

There are three broad kinds of transgenic manipulations: add genes, delete genes, or modify genes. With conventional animal breeding, we use the genetic variation that nature has provided, and continues to provide, for example by mutations. Most mutations are harmful with the net result of functionally deleting a gene. Sometimes a counter-intuitive result occurs such as deleting an inhibitor can result in stimulation. Another natural example is that some viruses end up adding genes from a different organism, resulting in a natural transgenic change.

In any case, transgenic manipulations usually result in increasing the genetic variation. An examples is modifying a gene for lysozyme so that it is expressed in the mammary gland. Lysozyme is a naturally occurring molecule that is antibacterial, and for example is secreted in tears. Transgenic modifications often concern the so-called regulatory part of a gene. This specifies how active the gene is, in which tissue, and under what circumstances. In the transgenic lysozyme example, a new gene is not added, but rather it is expressed in an additional tissue. A non-transgenic example of regulating gene expression is the prolactin receptor in mammary tissue. While both males and females have this gene, it is only expressed in female mammary tissue when lactation is appropriate. Similarly, the genetic components of the growth hormone system are more active in growing individuals than mature ones.

Transgenic procedures have great promise, and likely will be used extensively in agricultural animals in the future, just as they are currently used in plants. For example, the lysozyme example in milk likely would lead to less mastitis. Another example is adding the polled gene to breeds with horns. The polled gene often is introgressed from other breeds by making half-bloods, 3/4 bloods, etc., but this is an expensive and time-consuming process.

One neat idea is to combine transgenics and sexed semen by having genes for extra growth on the Y-chromosome. Such males will grow faster and larger, but females will stay smaller. You then have both maternal and terminal cross characteristics in the same strain of cattle and breeders could use X-sperm for female replacements and Y-sperm for males for terminal crosses. One would need to regulate the genes for growth so that they are expressed after birth to keep birth weights low.

The actual transgenic modifications are usually made to embryos, and the procedures are complicated and very expensive. However, the transgenic changes are transmitted to future generations. Thus, for example, offspring from a transgenic bull will also have the transgenic modification, and in turn will transmit it to their progeny.

There are hundreds of possibilities for useful transgenic manipulations. We do need to be careful not to have inappropriate side effects, but that is true for any breeding practice. An example from years ago was breeding Angus or Hereford heifers with semen from the newly introduced European breeds, resulting in severe dystocia in many cases. There obviously will be some trial and error with any new technology, so procedures need to be put in place to minimize problems, especially concerning animal welfare.

Mass production of embryos

Several centers, mostly in other countries, produce over 10,000 in vitro-produced embryos annually, and with slaughterhouse ovaries, huge numbers can be produced quickly. With cloning, for example, the genetics of the recipient oocyte has little influence on the genetics of the clone, and for some applications, the genetics of the sperm is much more important than the genetics of the oocyte.

It certainly is theoretically possible to have a mass production system that would make these procedures relatively inexpensive, although there always will be costs associated with the recipient herd; nevertheless, transfer of frozen embryos is not greatly more complicated than artificial insemination.

One example of such a system is used in Japan, where beef from Wagyu cattle is very valuable. They slaughter heifers and keep the ovaries from those with the best carcasses; aspirated oocytes plus sperm from proven bulls result in embryos that will produce superior carcasses. The carcasses of those animals for meat are worth 3 to 4 times the value of average carcasses in the United States, which makes this system feasible.

Keeping track of dozens of individual donors and semen from numerous bulls plus then keeping the container with the resulting developing embryos correctly labeled requires a well designed tracking system. Use of bar codes plus bar code readers and computers is one approach.

Some people have speculated that such mass production systems could be developed to produce embryos for less than $10 each. In fact, many research laboratories already do that. However, the ovaries are from slaughterhouses, and it is not necessary to keep track of individual donors. It is difficult to envision a commercial system for beef cattle in North America in which the identity of the oocyte donor is lost in the process, and that would be economically viable within the next decade. However, further into the future, it may be possible to generate huge amounts of information on individual embryos so as to guarantee not only genetic information such as sex, polled status, calving difficulty, etc., but in addition, that the embryos will result in average pregnancy rates exceeding 80% after nonsurgical embryo transfer. Incidentally, the pedigree of the embryo will be of little value compared with knowing its exact genetic make-up.