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Biochemical Effects of Recombinant Porcine Somatotropin on Pig Fetal Growth and Metabolism: A Review

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Abstract: Prenatal development is mainly dependent on a close interrelation between nutritional supply use and regulation by hormones and growth factors. Mechanisms during early embryonic development are sensitive to manipulation through selected management strategies of the sow and modifications of this strategy may serve as a model for the examination of molecular and cellular events controlling early embryonic growth. The administration of growth hormone (GH) to pregnant sows affects the development of fetuses in a manner dependent on the gestational period of treatment, therefore suggesting that maternal GH plays a significant role in prenatal development. In addition, in well-fed and feed-restricted gilts, treatment with porcine somatotropin (pST) during early to mid-pregnancy promotes the growth of their placenta and/or fetuses. Due to an exponential increase in research exploring the role of ST in growth biology, collectively, these studies resulted in an unprecedented increase in our understanding of how ST affects growth of domestic animals. Thus, the main purpose of this review is to provide an overview of the remarkable biological effects that pST has on pig fetal growth.

Key words: prST, gestation, fetus, sow, placenta

INTRODUCTION

A wide range of biotechnology strategies for altering the balance between lean and adipose tissue growth and deposition in meat-producing animals are available. These include genetic selection and husbandry (production) strategies. More recently, the confirmation of the growth-promoting and nutrient repartitioning effects of somatotropin, somatomedin, β-adrenergic agonists, immunization of animals against target circulating hormones or releasing factors and gene manipulation techniques, have given rise to a technological revolution for altering growth and development in meat producing animals[1].

Growth is a complex phenomenon, influenced by many determinants[2], it is clear from experimental studies that a range of molecular, cellular, metabolic, neuroendocrine and physiological adaptations to changes in the early nutritional environment, result in a permanent alteration of the developmental pattern of cellular proliferation that may result into adverse health consequences in adult life[3]. Fetal growth rate is sensitive to the rates of placental delivery of nutrients and oxygen from maternal to fetal blood. This supply varies with the availability of circulating nutrients in the mother and with the efficiency of their transfer by the placenta to the fetus[4]. This is important for swine producers since it is well known that birth weight of piglets has a great impact on neonatal survival and subsequent growth performance of pigs[5].

Recent attempts to improve production efficiency in domestic animals have addressed the use of exogenous somatotropin administration[6]. So far, the mechanisms underlining the increased fetal growth in response to maternal porcine somatotropin (pST) treatment have not yet been established[7]. In addition, pST treatment has been reported to have both

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stimulatory and inhibitory effects on reproductive functions in gilts[6].

There is a growing database supporting the use of pituitary or recombinant derived porcine somatotropin (rpST) as an agent to improve efficiency of growth and carcass composition in swine[1]. Many studies have shown that administration of exogenous pST to pigs markedly improves growth rate, efficiency of feed utilization and carcass leanness[1,8], decreases adipose tissue accretion and increases protein deposition[9]. This suggests that pST may have direct effects on myofibers or alternatively, that ST regulates the synthesis of insulin-like growth factor I (IGF-I) in skeletal muscle of growing pigs[9].

One of the many actions of ST is to stimulate hepatic production of IGF-I and IGF binding factor-3 (IGFBP-3), as well as the rate of growth of lean tissue[10,11]. IGFBPs can modify IGF activity by binding IGFs and preventing IGF receptor activation. It is also possible that IGFBPs have actions that are independent of their roles as proteins that bind IGFs[12]. In experiments with growing-finishing pigs, it is well documented that the administration of pST stimulates IGF-I synthesis in liver and other tissues and significantly increases plasma glucose, free fatty acids and insulin[13]. It has also been reported that administration of porcine GH during gestation and lactation or during lactation only has shown to increase milk production of sows by >16% in the 3rd or 4th week of lactation and improved traits related to blood glucose homeostasis of newborn pigs[14]. It has been suggested that these factors and their interactions are important in regulation of fetal growth. Direct actions of nutrients together with indirect growth factor-mediated mechanisms are probably involved in maternal growth hormone action on prenatal growth[15].

The administration of GH to pregnant sows affects the development of fetuses in a manner dependent on the gestational period of treatment, therefore suggesting that maternal growth hormone plays a significant role in prenatal development[16,17]. In addition, in well-fed and feed-restricted gilts, treatment with pST during early to mid-pregnancy promotes the growth of their placenta and/or fetuses[4,17].

Due to an exponential increase in investigations exploring the role of ST in growth biology, collectively, these studies resulted in an unprecedented increase in our understanding of how ST affects growth of domestic animals. Thus, the objective of this review is to provide an overview of the remarkable biological effects that ST has on pig fetal growth.

Fetal growth: Normal fetal growth involves an increase in cell number during embryonic and fetal development, followed by an increase in cell size. Fetal growth and development has genetic as well as environmental influences. Uterine capacity is a measurement of the ability of the uterus to support embryos and fetuses through gestation. Physical, biochemical and morphological limitations to uterine capacity include space, nutrients, gaseous exchange and placental surface area[18]. Fetal growth seems to be affected by the balance of macronutrients and not only by the amount of protein included in the maternal diet[19]. Fetal growth rate is sensitive to the rates of placental delivery of nutrients and oxygen from maternal to fetal blood. This supply varies with the availability of circulating nutrients in the mother and with the efficiency of their transfer by the placenta to the fetus[4]. Conditions that reduce the availability of substrates or those that reduce nutrient delivery across the placenta can retard fetal growth[20,21]; severe maternal undernourishment reduces birth weight in humans[22,23]. On the other hand, increased fetal nutrient uptake is accomplished either by enlarging placental surface area or increasing placental vascularity[24].

The growth promoting and anabolic actions of GH are mediated by insulin like growth factors (IGF-I and IGF-II) acting in both as endocrine and paracrine manner[25]. According to Chastant *et al.*[26], these insulin-like growth factors play an important role in embryonic and fetal growth, especially in the pig. IGF-I and IGF-II have a key role in regulating fetal-placental growth throughout gestation. Indeed, they have metabolic, mitogenic and differentiative actions in a wide range of fetal tissues including the placenta[10]. They act as progression factors in the cell cycle and increase DNA synthesis and cell differentiation in cultured embryos and several different fetal cell lines *in vitro*. Their concentrations in the fetus *in vivo* are positively correlated to birth weight in a number of species including humans, primates, sheep, pigs, rabbits and rodents[27].

In the placenta, expression of the IGFs is species-specific. The rodent placenta expresses only the IGF-II gene while the placenta of guinea pigs, ungulates, human and non-human primates express both IGF genes[27]. Fetal IGF concentrations are also affected by the endocrine environment *in utero*, particularly by nutritionally sensitive hormones known to regulate fetal development, such as insulin, thyroxine and glucocorticoids. Like nutrient restriction, deficiency of these hormones *in utero* affects expression of IGF-I more readily than IGF-II. Compared to the adult, GH has relatively little effect on the IGF axis in the fetus, probably due to the paucity of GH receptors in fetal tissues for most of gestation[27].

Somatotropin is an important modulator of insulin sensitivity and both are important regulators of cellular and whole body metabolism as well as somatic growth and body composition. ST counteracts the action of insulin on glucose homeostasis in both humans and animals and a significant impairment of glucose metabolism may be observed after exogenous administration of ST in physiological or pharmacological doses in humans[28]. GH is not able to

cross the placenta, but elevated GH in pregnancy may promote fetal growth either by increasing maternal plasma glucose concentrations through its antagonistic effects on insulin action or by increasing placental capacity to transfer nutrients[4]. Fetal availability of nutrients is however, regulated by a more complex hormone regulation than the interaction between ST and insulin. Maternal ST and IGF seem to be key determinants of fetal growth and birth weight[29]. In addition, placenta produces a variant of ST which progressively replaces pituitary ST in the maternal circulation from mid-pregnancy[30].

The embryonic growth during this period of development is determined mainly by nutrition and tissue growth factors (uterine, placental, embryonic) that in turn are under the influence of circulating maternal hormones and growth factors. Moreover, insulin growth factors (IGF-I and IGF-II play an important role in embryonic and fetal growth, especially in the pig. In order to determine whether IGFs might be involved in pig embryo development, Chastant *et al.*[26], looked for the presence of IGF-I and IGF-II/manose-6-phosphate (M6F) receptors in pig embryos during the preimplantation period, from the four-cell stage up to the beginning of blastocyst elongation, by both immunohistochemistry and autoradiography experiments. The authors could only detect IGF-II/M6F receptors on porcine trophectoderm cells on whole embryos at days 4 and 6 of pregnancy, on embryo sections at days 8 and 10 and on fetal and maternal compartments of the placenta at day 20 of pregnancy.

Somatotropin release and effects: The growth hormone, somatotropin is a protein hormone of about 191 amino acids that is synthesized and secreted by somatotrophs in the anterior pituitary in response to the hypothalamic peptide, GH-releasing factor[31]. Somatotropin is a major participant in control of several complex physiologic processes, including growth, metabolism, protein synthesis and cell proliferation. Indeed, it is the most important peptide hormone affecting growth. In 1945, GH was isolated from anterior pituitary and experiments evaluating the effects of crude preparations of porcine growth hormone began in pigs[32]. ST release from the anterior pituitary gland is regulated by hormones produced in the hypothalamus. ST release is stimulated by growth hormone releasing hormone (GHRH) and decreased by somatostatin, a GH-inhibiting factor.

Porcine somatotropin is naturally produced in pigs and treatment of growing pigs with exogenous pST significantly improves their growth rate, carcass composition and growth efficiency while reducing feed consumption and fat deposition[33,34]. Historically, pST was derived from the pituitary glands of slaughtered pigs, limiting the available quantities and setting the price correspondingly high. More recently, recombinant DNA technology has allowed expression of pST in microorganisms and cultured cells. pST cDNA prepared using poly(A) mRNA from pituitaries was first bacterially cloned in 1983, followed by pST expression in a variety of *Escherichia coli* prokaryotic expression systems[31]. Thus, large quantities of high-purity pST may be obtained.

The primary role of GH is promotion of linear growth. Treatment of pigs with pST increases protein accretion and decreases fat deposition in boars, barrows and gilts in both poor and improved genotypes[32]. This somatotropic effect is mediated partially through stimulation of the synthesis of IGF-I in the liver and in the growth cartilage where it acts as a local paracrine-autocrine hormone. However, GH continues to play an important physiologic and metabolic role long after final height has been reached. GH production is maintained throughout life where it has diverse metabolic actions, including anabolic, lipolytic and diabetogenic effects. Normal aging is associated with a great decline in GH secretion accompanied by a decrease in bone density and muscle mass and an increase in adipose tissue[35]. Treatment of pigs with pST has been reported to reduce chondrocyte metabolism and compromise cartilage, bone and joint development in growing animals[36].

GH has anti-aging properties and short-term administration of GH stimulates protein synthesis, increases lean body mass and accelerates bone turnover. It also causes insulin antagonism and alters total body water. However, the most dramatic metabolic effect of GH is lipolysis and loss of visceral adipose tissue[35].

Somatotropin in fetal growth: Fetal growth is increased when pregnant gilts are treated with rpST[37]. Treatment of pigs with pST in early to mid-pregnancy increases body weight and length of their fetuses by mid-pregnancy, but this increased weight may not persist to birth[7]. Intrauterine growth retardation is associated with lower than normal concentrations of GH and IGF-I in maternal plasma in humans[38]. In pigs the degree of late fetal development and maturation is an important predisposing factor for stillbirth and preweaning mortality and involves characteristics like placental functioning, functional maturity of vital organs and availability of body energy reserves[39]. Fetal growth is dependent on the hormonal status of the dam; maternal pST treatment may affect the environmental conditions for embryonic and fetal growth both in a direct manner via nutrient supply and in an indirect manner by secondary changes at the level of the placenta and (or) by an induction of growth factor release[40]. According to Gatford *et al.*[41], maternal nutrition and growth hormone treatment during early- to mid-pregnancy can each alter the subsequent growth and differentiation of muscle in progeny. In addition Etienne *et al.*[42], demonstrated an improved postnatal survival of pigs in sows with enhanced plasma GH concentrations.

The mechanism (s) for promotion of fetal growth by pST treatment during pregnancy is (are) not clear. It is possible that pST may promote the growth and functional development of the placenta. It is also possible that pST changes maternal metabolism in ways that support increased nutrient transfer to the fetus. In contrast, the pig placenta is epitheliochorial and does not significantly invade the endometrium and the pig lacks placental lactogen or placental growth hormone. Circulating somatotropin does not rise and circulating levels of IGF-I fall during pregnancy in the pig, implying that these hormones do not regulate maternal metabolic adaptations to pregnancy in this species, although there is some evidence for paracrine activity of this axis within the placenta. Nevertheless, changes in maternal metabolism probably account for much of the increase in fetal growth during maternal pST treatment in the pig. In the well fed and in the feed-restricted pregnant gilt, pST treatment during early to mid-pregnancy enhances the deposition of lean tissue and reduces fat deposition and increases maternal plasma concentrations of IGF-I[4,17].

Rehfeldt *et al.*[16], administering ST (6 mg) to sows at different gestational ages, observed that its administration during early pregnancy (day 10 to 24) induced the formation of significantly more muscle fibers (27%) in the semitendinous muscle of fetuses. When given from days 50 to 64 of gestation there were no beneficial effects on fetal development; and administered from days 80-94 there were higher body weights and advanced stage of maturity at birth.

Recombinant porcine somatotropin in early gestation: According to Rehfeldt *et al.*[40], maternal ST is an influential factor in early pregnancy capable of affecting the basic events of myogenesis. Administration of pST from day 10 to 27 of gestation (6 mg), increased the total number of fibers (primary and secondary fibers) in neonatal semitendinous muscle of middle and low weight littermates. ST induced increases in muscular protein concentration, creatine kinase activity, muscle fiber girth, as well as type II and type I fiber conversion which revealed an advanced degree of differentiation at birth.

Preliminary results had shown no effects on pregnancy rate, embryonic survival and number of normal embryos at 25 days after mating[43]. However, Kelley *et al.*[44,45], observed that supplying GH (15 mg kg^{-1} body weight) twice daily during days 28 to 39 of gestation, increased embryonic survival from 77.0 to 87.9% and embryos from treated sows had increased crown-rump lengths at 40 days of gestation. Nevertheless, there were no differences in weight of embryos, maternal uterine weight or uterine horn length at 40 days. It seems that early development processes of the embryo may be sensitive to increased GH concentrations at specific time periods in the pregnant sow. More recently, Gatford *et al.*[7], in maternal long treatment with pST (2 or 4 mg pST/day) from day 25 to 50 of pregnancy observed no effect on the number of piglets delivered per gilt (10.6 ± 0.3), the number of live-born piglets per litter (10.1 ± 0.1), or the number of stillborn piglets (0.5 ± 0.1) per litter ($P > 0.20$ for each). Nevertheless, birth weight and abdominal circumference of individual progeny at birth were all negatively correlated with litter size, were increased by treatment with pST during pregnancy, were not significantly affected by protein content of diet during pregnancy and were greater in male than in female progeny.

Litter size is determined by either ovulation rate (adjusted for potential embryonic viability) and/or uterine capacity[46]. Increasing ovulation rate has had limited effects on litter size because increased fetal death occurs if uterine capacity is exceeded during gestation[18]. According to these authors administration of rpST increased maternal IGF-I concentrations and placenta surface area but failed to increase fetal growth in a unilateral hysterectomy-ovariectomy model; therefore, mechanisms that are independent of maternal IGF-I or placental contact area may control early fetal growth under crowded uterine conditions.

According to Gatford *et al.*[7], treatment with pST before mid-pregnancy did not affect the number of piglets born per litter but independently increased body weight by 11.6% ($P < 0.001$) and length by 3.4% ($P = 0.005$) of progeny at birth and decreased ($P < 0.01$) the negative effect of litter size on body weight at birth.

In another study, Rehfeldt *et al.*[15], observed that birth weight of the smaller littermates was increased resulting in more balanced litters and the body composition of newborn piglets was affected when pST was given to gilts from day 10 to 27 of gestation. These changes were associated with increases in the number of skeletal muscle fibers in low and middle weight littermates, which was suggested to influence postnatal lean growth. Suggesting that growth conditions were selectively improved for the smaller littermates and that the conditions for the middle and heavy ones were adequate or not limited by maternal somatotropin. This is consistent with results reported previously by Sterle *et al.*[17], demonstrating that the effect of pST was more pronounced on growth of small fetuses with shorter length of the placental contact area (respective vascular area of the uterus). Therefore, the increase in birth weight of the smaller littermates may enhance their chance of survival and improve their growth rate. In addition, authors suggested that rpST treatment during gestation had a greater effect (increased weight) on fetuses with shorter implantation lengths.

Kuhn *et al.*[47], showed that sows injected daily with 6 mg pST/day between days 10 to 27 of gestation and subsequent withdrawal up to day 37 of gestation by decreasing dosages, had higher birth weights in low weight littermates, whereas it remained almost unchanged by pST treatment in high weight piglets.

They also concluded that the heavy littermates had the lowest advantage of pST treatment and related increase in nutrient availability for the prenatal growth. In this study, the birth weight of high weights piglets tended to be even reduced, but it was increased again in low weights piglets. Consistently, birth weight became more balanced within the litters in response to early pST treatment. In a similar study with injections of sows with 6 mg pST/day between days 10 to 27 of gestation, by Schneider *et al.*[48], daily maximal ST concentrations were clearly different between rpST-treated and control gilts and were not different over the various days of intensive blood sampling; the mean circulating IGF-I concentrations were stable in control animals during the whole experiment, however, an increase in plasma concentration of IGF-I was observed in treated animals (P <0.001). In addition, mean insulin concentrations were higher in rpST-treated gilts on day 14 of gestation (P <0.05) and were also numerically greater on days 10, 12 and 18, without being significant (P = 0.22, 0.23 and 0.29, respectively) because of high standard errors. In this study, concentrations of both FFA and glucose were greater during rpST treatment. These observations support the hypothesis that prolonged ST treatment tends to create a diabetic response. It is well known that ST stimulates lipolysis and mobilization of stored triglyceride as FFA and glycerol. Glycerol contributes to gluconeogenesis while FFA are both oxidized directly and converted to ketone bodies and then oxidized. The hyperglycemia observed resulted from an increase in hepatic glucose output and a concurrent impairment in glucose clearance.

Rehfeldt *et al.*[15], showed that pST treatment leads to higher nutrient availability to the embryo, the concentrations of glucose and free fatty acids were determined in the fluids. Sterle *et al.*[37], observed that an increased fetal growth may result from a somatotropin- or IGF-I-mediated endocrine mechanism that may stimulate fetal growth or change nutrient availability to the fetus. Although other mechanisms are also possible, including altered expression of other fetal or placental growth factors.

Maternal pST treatment increased fetal plasma concentrations of glucose at day 51 of pregnancy in restrictedly fed gilts[4], consistent with increased delivery of glucose to the fetus in response to elevated maternal glucose levels produced by pST treatment of pregnant mothers. Maternal pST treatment from day 10 to 27 of pregnancy in well-fed gilts increased maternal plasma concentrations of glucose and free fatty acids (FFA)[48] and this was associated with increased glucose concentrations in allantoic and amniotic fluids at day 28 of pregnancy[15]. On the other hand, maternal hyperglycaemia increases placental glucose transfer and birth weight in humans[49]. Ezekwe and Martin[50], reported that the hyperglycaemia of maternal diabetes may have been primarily responsible for the increased lipid deposition in the fetus. Maternal diabetes has also been shown to increase liver weight and total liver glycogen, as well as to improve pig survival and maintenance of serum glucose and FFA levels during a fast[51]. Similar trends with respect to increased pig body lipids, liver glycogen concentrations and serum glucose and FFA levels were observed in the study of Kveragas *et al.*[52], for pigs from GH-injected dams.

Gatford *et al.*[4], observed that the maternal plasma concentrations of IGF-I were increased three-fold by pST treatment at 25.6 μg kg^{-1} day in early gestation. Maternal plasma IGF-II (65·3_2·8 nmol L^{-1}) and insulin (22·9_4·0 IU mL^{-1}) concentrations were not affected by pST administration and fetal weight (body weight, liver weight) and size (length, biparietal diameter) were increased by pST treatment of mothers.

Maternal GH treatment also stimulates hepatic IGF-I synthesis and this IGF-I may affect placental growth or function via placental IGF-I receptors[26]. Sterle *et al.*[17], reported an increase in placental as well as fetal weight in response to maternal GH treatment of pregnancy in pigs and suggested that fetal growth was increased in part by enhancing placental size and transport capacity. It is possible that placental function was enhanced by maternal GH treatment in this study, at least at the lower dose of GH used, since fetal plasma glucose concentrations were increased and maternal/fetal glucose gradient was decreased in gilts treated with 13.4 μg pGH kg^{-1} day. However, fetal weight was not correlated with fetal plasma glucose or the maternal/fetal glucose gradient, implying that glucose is not the nutrient which limits fetal growth in the undernourished pregnant pig and that improved placental glucose transport was not the major mechanism for increased fetal growth in response to maternal GH treatment. Gatford *et al.*[4], suggested that maternal GH treatment increased fetal growth by increasing availability to the fetus of an alternative growth-limiting nutrient, probably via increased maternal plasma concentrations. Fetal growth was increased and plasma concentrations of urea were decreased in fetuses from sows treated with two doses of pST (13.4 and 25.6 micrograms/kg live weight), from day 25 to day 51 of pregnancy, suggesting that protein catabolism may be decreased in these fetuses and that the supply of alternative fuels for oxidation is increased by both doses of pST. The concentrations of free fatty acids in maternal plasma at day 51 of pregnancy were decreased and maternal plasma concentrations of glucose, urea and triglycerides were unaltered by GH treatment. Maternal plasma alpha-amino nitrogen concentrations were positively correlated with GH dose and with fetal weight, suggesting that GH treatment may increase fetal growth by increasing the supply of one or more amino acids which limit fetal growth.

Rehfeldt *et al.*[15], showed that nutrient supply to the embryo was improved. Glucose concentrations in amniotic and allantoic fluids were significantly

increased by pST action at day 28 of gestation (P □0.05). Moreover, the increased volume of allantoic fluid at the end of treatment indicates higher nutrient (such as glucose, free fatty acids and amino acids are directly available to the embryo by transporter-mediated placental transfer) turnovers in response to elevated maternal pST. With pST treatment during day 10 to 27 of gestation, nutrient concentrations in maternal blood were markedly increased and subsequently the embryo was exposed to an excess (20 to 35%, compared with controls) of substrate whereas IGF-I concentration was increased 5- to 6-fold of control[53]. Rehfeldt *et al*.[15], results are consistent with the dependence of uteroplacental glucose transport on the maternal glucose concentration. The same is true for free fatty acids, although the mechanisms for transfer are more complex. Substrate availability is the main critical factor for fetal growth and maternal glucose is the primary energy producing fuel. Sterle *et al.*[17], suggested an increased uptake or utilization of nutrients by fetuses in response to maternal pST treatment.

According to Sterle *et al.*[37], gilts treated with 5 mg rpST from day 30 to day 43 of gestation had heavier fetuses and placentas, but increased fetal growth was not associated with changes in IGF or IGFBP-2 mRNA concentration in reproductive tissues, concluding that other mechanisms, therefore, lead to enhanced fetal growth in somatotropin-treated pregnant sows.

Recombinant porcine somatotropin in late gestation: According to Rehfeldt *et al.*[16], maternal pST treatment of shorter duration in late pregnancy has little or no effect on progeny weight at term, however, progeny birth weight was increased by only 5% following maternal treatment with 6 mg pST/d from day 80 to 94 of pregnancy and elevated maternal plasma GH in the last 2 or 3 week of pregnancy did not increase progeny weight at term[42,52]. More recently, Trujillo-Ortega *et al.*[54], findings confirmed that rpST administered in late pregnancy favors fetal growth in pigs. The increased neonatal size was consistent with that reported elsewhere[7,16]. rpST administration in late pregnancy to primiparous sows increased the rate of neonatal deaths and was associated with higher blood glucose levels both in sows and piglets[54]. In this latter study, more meconium-stained piglets were born in the rpST group, which may reflect the difficulties of delivering them.

Gatford *et al.*[7], observed an increase in birth size following 75 days, but not 25 days of maternal pST treatment, suggesting that somatotropin promotes fetal growth mainly via changes in maternal metabolism that increase nutrient availability to the fetus and that any effects of pST to increase placental growth or function are not capable of sustaining increased fetal demand for nutrients if pST treatment ceases in mid-pregnancy. Cromwell *et al.*[8], observed that daily administration of porcine somatotropin before farrowing in a warm or hot environment may result in increased susceptibility of sows to heat stress.

Growth hormone releasing factor stimulated GH secretion in sows during late gestation. The GHRF treatment (50 mg kg^{-1}) of sows during late gestation increased (P<0.05) pregnancy duration by approximately 1 day. The number of pigs born, born alive and stillborn per litter and pig mean weight at birth were not affected[42]. Elevated sow blood glucose resulted in significantly increased fetal body fat percentages and liver glycogen concentrations[50], which are important aspects of baby pig survival[55]. Pigs born from GHRF-treated sows were approximately 1 day older at birth and may have been more mature and more active and the GHRF-treatment itself could improve pig maturity. Indeed, GH treatment of sows during late pregnancy has been show to increase concentration of glycogen in liver and carcass and total lipid content of newborn pigs. The authors postulated that GRF could have also acted directly on the development of the piglets via increased liver glycogen (induction of diabetogenic state) or body fat. Daily injections of sows with pST during the last 14 (5.8 mg) or 21 days (10 mg) of gestation resulted in hyperglycaemia[43]. Moreover, implanting sows with osmotic mini-pumps delivering 5 or 15 mg pST daily from day 94 of gestation to farrowing, did create a hyperglycemic state in sows. This lead to a tendency for greater glucose concentrations in newborn piglets, however, no consistent or reproducible increase in birth weight or performance of piglets from treated sows were observed[43].

Data from Kuhn *et al.*[47], confirm the hypothesis that maternal somatotropin is an influential factor for the development of the pig fetus and for postnatal growth. Maternal pST treatment in early to mid-pregnancy increases fetal growth but, unless pST treatment is continued, does not increase progeny size at birth. Maternal pST treatment that is continued from early to late pregnancy increases progeny size at birth and has the biggest effects in the largest litters[7]. These authors did not observe changes in fetal plasma IGF-I or IGF-II in response to maternal pGH treatment, despite increases in fetal growth. This suggests that maternal GH administration at low doses increased fetal growth through improved nutrient availability to the fetus, without nutritional modulation of the fetal endocrine IGF axis, at day 51 of gestation.

Effects of maternal pST treatment on placental function have not been assessed in pigs, but somatotropin increases placental capacity for transplacental diffusion of solutes in the late pregnant sheep[56]. The increase in birth size following 75 days, but not 25 days, of maternal pST treatment in the study of Gatford *et al.*[7], suggests that somatotropin promotes fetal growth mainly via changes in maternal metabolism that increase nutrient availability to the

fetus and that any effects of pST to increase placental growth or function are not capable of sustaining increased fetal demand for nutrients if pST treatment ceases in mid-pregnancy. Although pST treatment from day 0 to 30 of pregnancy in gilts with uterine crowding caused an increase in uterine-placental contact area that was maintained at least to day 65 of pregnancy, fetal size at day 65 was reduced by this treatment[18], also implying that altered placental structure is not the major mediator for the promotion of fetal growth by maternal pST.

The use of exogenous GH or GRF for sows during the last weeks of gestation in order to improve survival of piglets by increasing energy reserves in the fetuses does not seem very promising. However, the use of exogenous GH in earlier gestation to affect development of the embryos or fetuses seems more tenable[43].

Developing an effective means of increasing uterine capacity may increase litter size. Administration of recombinant porcine somatotropin during gestation has had variable effects that may be dependent on stage of gestation, duration of administration, reproductive age of female and environmental conditions and according to Sterle *et al*.[18], it has not been established whether these effects will persist to parturition. Cost considerations are the major limiting factors of wide spread use of GH therapy in resource-poor settings.

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