Chapter 4
Young Maternal Age, Body Composition and Gestational Intake Impact Pregnancy Outcome: Translational Perspectives

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Abstract Birth weight is a robust predictor of health and well-being immediately after delivery and throughout the life course. Maternal body composition at conception and gestational intake thereafter impacts prenatal growth velocity and birth weight irrespective of maternal age, but the most pronounced risk of poor outcome is when pregnancy coincides with adolescence and continued or incomplete growth of the mother. Experimental ovine paradigms have helped define the impact of nutrition in mediating pregnancy outcome in young adolescents. Low maternal nutrient status at conception has a modestly negative influence on placental growth and birth weight, but it is gestational intake after conception, particularly during the first third of pregnancy, which has the most profound influence on fetal development. Relative to optimally nourished controls, age-matched adolescents overnourished throughout pregnancy exhibit rapid maternal growth and increasing adiposity at the expense of the conceptus. Placental growth and vascular development, uteroplacental blood flows and fetal nutrient supply are compromised, and premature delivery of low birthweight lambs with a 45 % incidence of marked intrauterine growth restriction (IUGR) ensues. A more modest effect on fetal growth is evident in undernourished mothers (17 % incidence of IUGR). Here preventing maternal growth gradually depletes maternal body reserves and directly lowers nutrient availability in the maternal circulation independent of any change in placental size or gestation length. The maternal and placental adaptations to these diverse gestational intakes and the consequences for the fetus are presented together with the translational implications for detecting and avoiding birthweight extremes in human pregnancy.

Keywords Birth weight • Adolescent • Obese • Underweight • Placenta • Gestational weight change • Growth • Blood flow • IUGR

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4.1 Introduction

Birth weight is a valuable summation of prenatal fetal nutrient supply and a robust predictor of health and well-being immediately after delivery and throughout the life course. Of the infants born globally in 2013, and weighed at birth, an estimated 16 % were of low weight (<2500 g [1]), and even in relatively affluent countries such as the UK and USA, 8 % of infants were of low birthweight, including 0.9 % and 1.4 %, respectively, with very low birthweight (<1500 g [2–4]). The majority of very low birthweight infants are born prematurely, while those with modestly low birthweight (>1500 to <2500 g) are a mixture of early delivery and fetal growth restriction. Irrespective, relative to normal birthweight individuals, low birthweight infants born in wealthy countries are 25 times more likely to die within the first year of life [2, 4]. Infants that survive, irrespective of their country of birth, experience a range of physical and development issues that can limit their life chances. These include visual and aural impairment, autism, cerebral palsy, stunted growth, immune dysfunction, cognitive delay, behavioural problems and low educational attainment [5, 6]. Furthermore, low birthweight is a risk factor for diabetes, obesity, stroke, cardiovascular disease, immune dysfunction and osteoporosis in later life and several of these effects are exacerbated if the postnatal environment is nutrient rich such as occurs in populations undergoing economic transition and throughout the developed world [7–10]. At the other end of the weight spectrum, high birthweight (>4000 g) currently accounts for 7.4 % and 13.8 % of births in the USA and UK, respectively [3, 11]. Fetal macrosomia is a major risk factor for stillbirth, neonatal mortality (especially due to asphyxia), emergency delivery by caesarean section and infant mortality within the first year of life (especially due to sudden infant death syndrome) and is the predominant cause of birth injuries such as shoulder dysplasia: risks are most pronounced when weight exceeds 4500 or 5000 g [12–16]. High birthweight is strongly linked with the occurrence of an array of cancers throughout childhood, most notably leukaemia [17, 18]. Although less strong and more closely related to other biological factors such as birth length or adult height, positive associations between high birthweight and the incidence of breast, prostate, lymphatic, lung and colon cancer are evident in adult life [19–24]. Moreover, high birthweight is a risk factor for diabetes and obesity in later life and this relationship is variously influenced by maternal and paternal anthropometry and family history of diabetes [25–27].

Accordingly, avoiding birthweight extremes by increasing the proportion of babies born at a healthy weight is a pressing public health objective at individual government and world health organisation levels. The age, body composition and nutritional status of the mother at conception and her gestational intake thereafter plays an important and theoretically modifiable role in determining prenatal growth velocity and hence birth weight and is the focus herein.

4.2 Adverse Pregnancy Outcome: Who Is at Risk?

Across the world, the categories of women most readily identified as being vulnerable to poor pregnancy outcome are young adolescent mothers (<19 years old) and those of all ages who are either underweight or obese at the time of conception. For example, in Scotland these groups of women currently account for 10 %, 3 % and 18 % of all births, respectively [3]. In Sub-Saharan Africa, ~50 % of births are in adolescent mothers [28]. In this region, maternal underweight (17 %) rather than obesity (5 %) dominates in the general obstetric population, although obesity rates are rising [29].

4.2.1 Maternal Body Composition at Conception

Irrespective of the relative proportions in specific geographical locations, women who are underweight at conception are at greater risk of premature delivery, low birthweight and small for gestational age (SGA, birth weight <10th centile after adjustment for gender and gestational age) delivery [30–32]. At the opposite end of the body composition spectrum, maternal obesity is typically associated with a number of risks that generally increase stepwise with degree of overweight, namely hypertensive disorders (including pre-eclampsia), gestational diabetes, thromboembolism, fetal death, stillbirth, premature delivery, high birthweight and large for gestational age (LGA, birth weight >90th adjusted centile: [30, 33–36]). Obese women are also more likely to have an induced labour and to deliver their babies by either elective or emergency caesarean section. More rarely and somewhat paradoxically, obese women are also found to be at greater risk of both actual [37] or relative fetal growth restriction [38] which largely becomes apparent when customised birthweight centiles based on maternal weight, height, ethnicity and parity are used to define SGA [39]. Further, there are known associations between maternal obesity (independent of diabetes) and fetal malformations including spina bifida, anencephaly, congenital heart defects and orofacial clefts: these defects are often challenging to detect prenatally due to poor sonographic visualisation owing to the density of maternal body fat depots [40]. It is unsurprising that this myriad of pregnancy complications associated with a mother's BMI at conception results in a greater number and duration of maternal and neonatal admissions with associated health-care costs [41, 42].

Dietary intake and hence gestational weight change during pregnancy have the potential to ameliorate or exacerbate the risks associated with being under- or overweight at conception and recommended gestational weight gains (GWG) by pre-pregnancy BMI and for each period of pregnancy are available [43]. Although women who are underweight at conception commonly also display inadequate GWG, the converse is not always true. Thus, while ~70 % of obese women exceed current weight gain recommendations, there is also evidence that gestational weight

loss is more common in this group and increasingly prevalent as obesity severity increases [44, 45]. Irrespective, weight gain during pregnancy is an important independent predictor of birth weight [46], and in women with all categories of pre-conception obesity, the incidence of LGA robustly rises with increasing GWG and falls when GWG is inadequate. The converse is also broadly true with a decreased risk of SGA as GWG increased in obese women but with less potential benefit in the morbidly obese [46]. This summary data suggests that it may be safe to advocate GWG below current recommendations in obese women but when systematically examined obese women with GWG below the guidelines had a higher risk of both preterm delivery and SGA negating the benefits associated with a lower risk of LGA, hypertensive disease and caesarean delivery [47].

4.2.2 Young Maternal Age

Above all, the most consistent risk of poor outcome is when pregnancy coincides with adolescence. Relative to adult women, contemporary population-wide and single-centre cohort studies consistently report a higher risk of spontaneous miscarriage, premature delivery, low birthweight and neonatal mortality in adolescent pregnancies. These negative gestational outcomes are observed in low-, middle- and high-income countries and are particularly acute in very young girls who are gynaecologically and biologically immature [48–53]. Indeed, in low resource countries, biological immaturity also predisposes adolescent mothers to serious complications such as obstetric fistula [54], is associated with a plethora of maternal near miss events [55] and is a major factor contributing to the fourfold higher maternal death rate in very young mothers ($\leq$15 years) relative to both older adolescent (16–19 years) and adult (20–24 years) women [56].

Suboptimal dietary intakes are commonplace in the general adolescent population, and therefore many adolescent girls are in danger of becoming pregnant with poor nutrient stores and/or subsequently experiencing inadequate gestational weight gains. For example, relative to adolescents with a normal body mass index (BMI) at pregnancy booking, those classified as underweight (BMI $<$ 19) had a threefold higher risk of SGA birth [57]. In addition, low pregnancy weight gains in adolescent mothers have long been associated with a greater incidence of premature delivery, low birthweight and SGA that is variously dependent on the pattern of weight gain (early versus late versus all gestation) and age ($<$16 years versus 16–19 years) of the mother at conception [58–60].

Obesity has now overtaken underweight prevalence in most adolescent populations throughout the developed world [61] and hence the relationship between periconception obesity, gestational weight gain and pregnancy outcome in adolescent mothers is increasingly relevant. In single-centre and population-wide retrospective cohort studies involving ~700, 4822 and 34,648 adolescents delivering in three contrasting areas of the USA, being overweight or obese was typically associated with an increased risk of pregnancy hypertension, gestational diabetes

and impaired glucose tolerance, labour induction and caesarean section and was protective against premature delivery. Neonatal findings included higher average birthweight, greater incidence of macrosomia and more morbidity, while the prevalence of low birthweight and SGA was less common relative to normal BMI adolescents [62–66]. Some of the negative pregnancy outcomes were exacerbated by high gestational weight gains and influenced by race but on balance the effect of BMI, albeit based on self-reported pre-pregnancy height and weight, dominated. In direct contrast in a prospective observational study of adolescents based in the UK ($n = 368$), having a high BMI was linked to a threefold higher risk of SGA [57].

While the characteristics of adverse pregnancy outcome in adolescent mothers who are either underweight or overweight at conception are broadly similar to those described for adult women, the young adolescent mother is distinguished by the fact that she may still be growing or have the potential to grow at the time of conception. Although skeletal growth peaks before menarche, it can continue albeit at a slower rate into late adolescence. Accordingly, data from the Camden Adolescent Pregnancy and Nutrition Project (based in New Jersey, USA) indicated that continued maternal growth occurs in approximately 50 % of the pregnant adolescent population. This continued maternal growth as measured by sequential changes in knee height was associated with larger pregnancy weight gains and increased fat stores, but in spite of this the babies were 150–200 g smaller than those born to non-growing adolescents and mature women [67]. These effects attributed to a competition for nutrients between the maternal body and her gravid uterus [68] are supported by a large retrospective analysis of subjects ($n = 9694$) with similar pre-pregnancy weight range and term delivery, in which young adolescents (14–17 years) were shown to transfer a smaller proportion of their pregnancy weight gain to their fetuses than older adolescents (17–19 years) and adult (20–25 years) women [69]. A similar maternal–fetal growth competition for nutrients has been observed within a group of Peruvian adolescents (13–15 years). When adolescent growth status at delivery was defined on the basis of achieving parental height, the adolescent mothers who had not achieved their predicted adult height and therefore categorised as 'still-growing' had smaller babies than those who had achieved their expected growth [70]. In a more contemporary multicentre study in two socially deprived areas of the UK, a third of adolescent girls (average age 17.8 years) continued to grow during pregnancy and had higher gestational weight gains and fat accrual than non-growers [57]. Nevertheless and in contrast to earlier studies of younger adolescents, this was not associated with fetal growth restriction but rather an increase in LGA births. Alternatively, comparisons between non-pregnant and pregnant adolescents suggest that normal fetal growth can be maintained if pregnant mothers diminish their resting energy expenditure and cease growing to conserve nutrient supply for the fetus [71].

The relationship between nutritional status at conception, gestational dietary intake and pregnancy outcome is clearly appreciably more complex when pregnancy coincides with the continued or incomplete growth of the mother. It was against this background that a highly controlled sheep paradigm was originally

developed to examine the role of maternal nutrition in mediating pregnancy outcome in the young but still growing adolescent.

4.3 Nutrition, Growth and Pregnancy Outcome in Young Adolescent Sheep

4.3.1 Basic Adolescent Sheep Paradigm

The basic adolescent paradigm as developed in my laboratory involves assisted conception procedures to establish singleton pregnancies in peripubertal adolescent ewes of equivalent age, live weight and adiposity at conception. Adult ewes of known reproductive history and in prime breeding condition are superovulated and intrauterine inseminated by a single sire and act as embryo donors. Within individual studies the resulting grade 1 embryos for any given embryo donor are then distributed evenly across the study groups: this controlled approach minimises the impact of the main peri-conceptual factors known to influence feto-placental growth and maximises the genetic homogeneity of the resulting fetuses [72]. Adults are preferentially used as embryo donors as prior reciprocal embryo transfer studies revealed that embryos derived from adolescent ewes have inherently low viability following transfer into either an adolescent or adult uterus [73, 74]. Nutritional treatments typically commence immediately after embryo transfer and involve offering the young still-growing adolescent recipient varying quantities of the same complete diet to manipulate gestational weight gain and thereby growth and adiposity. In the overnourished model, this involves offering the adolescent mothers a high dietary intake throughout gestation (~2 × maintenance requirements) to promote rapid maternal growth and is designed to mimic pregnancy in adolescent girls who continue to grow significantly while pregnant. In contrast in the second and to date less well-studied undernourished model, the adolescent dams are prevented from growing while pregnant (low intake, ~0.7 × maintenance). The control group for both models involves a moderate dietary intake designed to facilitate a small amount of maternal growth (maintenance) and calculated to maintain maternal adiposity at a consistent level throughout gestation: this allows the estimated nutrient requirements for optimum conceptus growth to be met and is achieved by modest step-wise increases in maternal intake of control dams during the final third of gestation.

4.3.2 Pregnancy Outcome in Overnourished Adolescents

The overnourished model has proved extremely robust over many years and a summary analysis of pregnancy outcome in relation to maternal nutrition during

gestation was published a decade ago [75]. This revealed that high dietary intakes to promote rapid maternal growth were associated with an increased incidence of miscarriage and stillbirth in late gestation, and while mean placental and fetal growth were significantly reduced relative to controls, the degree of compromise was variable with 52 % of pregnancies classified as intrauterine growth restricted (IUGR). A summary analysis for the new trials carried out in the intervening period is presented in Table 4.1 together with indices of maternal anthropometry. A live born fetus spontaneously delivered at term was categorised as markedly growth restricted if its birth weight was two standard deviations below the mean birth weight of fetuses in the control group. As control group male fetuses were on average 287 g heavier than females, the categorisation used sex-specific cut-offs (IUGR birth weight, <4108 g for males and <3798 g for females) and on this basis 98 of 218 high intake pregnancies (45 %) were classified as growth restricted. Using this approach to subdivide the high intake (overnourished) pregnancies reveals that in the growth restricted category, placental weight and fetal cotyledon weight were reduced by 46 % and 58 %, respectively, relative to the control group, and associated with a 45 % reduction in birth weight. In contrast in the non-growth-restricted group, placental weight and fetal cotyledon weight were reduced by 17 % and 31 %, respectively, and lambs were on average 12 % smaller: although much less perturbed, feto-placental weights were still statistically lower than in the control group. The positive relationship between placental mass and birth weight is emphasised in Fig. 4.1a and is appreciably stronger in the IUGR pregnancies suggesting less of a functional reserve when the placental growth trajectory has been severely compromised. Another consistent feature of the overnourished pregnancies is a major reduction in gestation length with viable lambs being born as early as day 135 of gestation (term = 145 days, Fig. 4.1b). Although the average reduction in gestation length is slightly greater in the growth restricted compared with the non-IUGR pregnancies (~4.5 and 3.7 days, respectively, Table 4.1), it is the dam's nutritional intake and associated reduction in placental hormone concentrations (progesterone and oestradiol-17ß) which dominates and most likely underlies early delivery relative to the control group [76, 77]. Importantly, when birth weight is adjusted to a standard gestational age, the large differences in birth weight between groups remain. As sheep tolerate prematurity poorly, even small reductions in gestation length can have profound consequences for the smallest lambs. These are exacerbated by a major reduction in the initial yield (Table 4.1), nutrient composition and IgG content of colostrum in overnourished dams [78–80] and by the delayed formation of an adequate ewe–lamb bond. The colostrum yield at parturition is positively related to placental mass and thereby reflective of previously documented reductions in lactogenic hormones including those secreted by the placenta predominantly during the second half of gestation (placental lactogen, progesterone, oestradiol-17ß [76, 77, 81]). Lambs which fail to ingest sufficient quantities of quality colostrum in the early neonatal period are vulnerable to hypothermia and infection and more than 65 % of overnourished pregnancies detailed (Table 4.1) were deemed potentially at risk. Initially neonatal mortality rates were unacceptably high [72] and thus a proactive regimen of intensive

Table 4.1 Maternal anthropometry and pregnancy outcome in singleton-bearing adolescent sheep offered a moderate (control) or high nutrient intake (overnourished) throughout gestation and categorised according to fetal growth status after spontaneous delivery[¥]

	Maternal nutrient intake and fetal growth status[¥]			
	Control—normal	High—IUGR	High—non-IUGR	Significance[ß]
No. of pregnancies	97	98	120	
Weight at conception (kg)	44.2 ± 0.39	43.0 ± 0.63	45.1 ± 0.63	$P = 0.042$
GWG, d4 to d50 (g/day)	48 ± 3.2^{a}	286 ± 6.5^{b}	255 ± 6.0^{c}	$P < 0.001$
GWG, d50 to d95 (g/day)	109 ± 2.9^{a}	319 ± 6.3^{b}	316 ± 5.2^{b}	$P < 0.001$
Weight after delivery (kg)	56.9 ± 0.4^{a}	77.3 ± 0.70^{b}	77.7 ± 0.64^{b}	$P < 0.001$
*Adiposity at conception	2.3 ± 0.02^{a}	2.3 ± 0.02^{b}	2.4 ± 0.02^{b}	$P = 0.031$
Delta adiposity, d4 to d50	0.0 ± 0.0^{a}	0.3 ± 0.03^{b}	0.2 ± 0.01^{b}	$P < 0.001$
Delta adiposity, d50 to d95	0.0 ± 0.0^{a}	0.6 ± 0.02^{b}	0.6 ± 0.02^{b}	$P < 0.001$
Adiposity pre-delivery	2.3 ± 0.02^{a}	3.1 ± 0.03^{b}	3.2 ± 0.03^{b}	$P < 0.001$
Gestation length (days)	145.2 ± 0.18^{a}	140.7 ± 0.23^{b}	141.5 ± 0.17^{c}	$P < 0.001$
Birthweight (g)	5427 ± 76^{a}	3007 ± 69^{b}	4769 ± 55^{c}	$P < 0.001$
Male:Female	46:51	55:43	60:60	NS
[þ]Adjusted birthweight (g)	5405 ± 72^{a}	3166 ± 70^{b}	4989 ± 54^{c}	$P < 0.001$
Placental weight (g)	442 ± 12^{a}	238 ± 6^{b}	365 ± 9^{c}	$P < 0.001$
Fetal cotyledon weight (g)	146 ± 4.4^{a}	61 ± 2.1^{b}	101 ± 2.6^{c}	$P < 0.001$
Birth wt : cotyledon wt	39.6 ± 1.00^{a}	52.1 ± 1.16^{b}	49.9 ± 1.13^{b}	$P < 0.001$
Birth wt : Maternal wt. gain d4 to d95	859 ± 39.9^{a}	109 ± 3.4^{b}	182 ± 4.3^{c}	$P < 0.001$
Colostrum yield (ml)	497 ± 40^{a}	113 ± 10^{b}	202 ± 13^{c}	$P < 0.001$
[ɣ]No. with inadequate colostrum/kg fetus	24 of 91[a]	63 of 91[b]	77 of 117[b]	$P < 0.001$

Values are mean ± sem. Data from seven studies ([80, 82, 86, 107, 116] plus unpublished)

[¥]Lambs from overnourished pregnancies were classified as intrauterine growth restricted (IUGR) if birthweight was < two standard deviations below the mean sex-specific birthweight of the optimally nourished control group, i.e. <3798 g for females and <4108 g for males

[ß]From Anova followed by Tukey comparison. Within rows where superscript letters (a,b,c) differ, $P < 0.01$. Sex distribution and number of ewes with inadequate colostrum compared by binary logistic regression

*Based on external body condition score (5 point scale where 1 = emaciated and 5 = morbidly obese) and assessed by a single experienced operator across all studies

[þ]Individually adjusted to a standard gestation of 145 days on the basis of the formula; adjusted birthweight = weight at birth/1.01305 per day of gestation

[ɣ]Defined on the basis of requirement of 50 ml per kg fetal weight

GWG gestational weight gain

neonatal care including supplementary feeding and prophylactic antibiotics is required to ensure that the most premature and growth-restricted individuals survive.

Retrospective analysis of maternal anthropometry in adolescent dams fed ad libitum to promote rapid growth was used to identify the antecedents of fetal growth

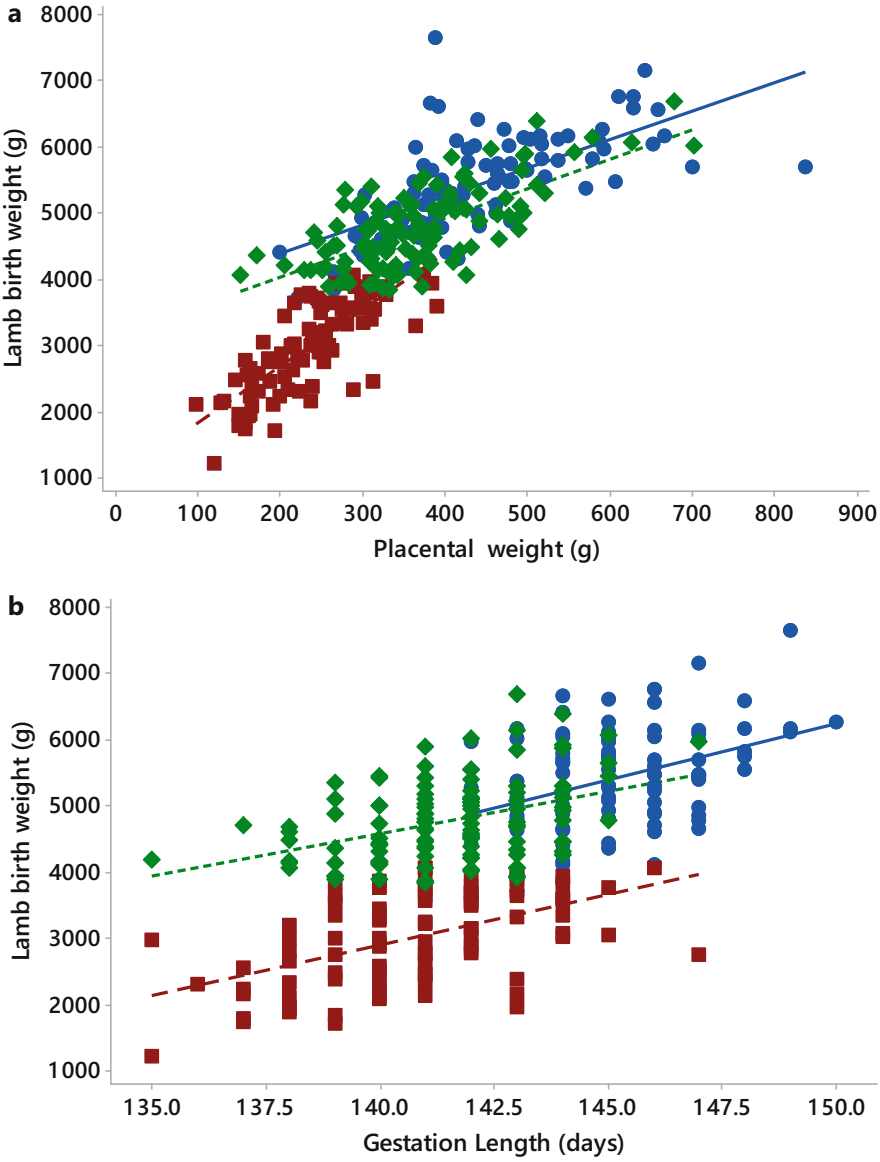

Fig. 4.1 Relationship between lamb birthweight and (**a**) placental weight and (**b**) gestation length in singleton bearing adolescent dams offered a control dietary intake to maintain maternal adiposity (*blue circles*) or a high dietary intake to promote maternal growth and adiposity throughout gestation. The latter pregnancies were categorised as intrauterine growth restricted (IUGR, *red squares*) or non-IUGR (*green diamonds*) using sex-specific birthweight cut-offs derived from the control group birthweight data as defined in the text

restriction. From an equivalent weight and adiposity at the time of conception, the dams allocated to the high intake group and subsequently delivering a growth-restricted fetus were very slightly lighter and leaner at conception than dams delivering a non-IUGR fetus (Table 4.1). However, the most striking difference between these groups was in the rate of weight gain during the first third of pregnancy (High-IUGR > High-Non-IUGR > Control). This is consistent with an early impact of maternal dietary intake on the development of the placenta (see below). Furthermore, the birth weight to maternal weight gain ratio serves to illustrate that the adolescent dams that grow fastest during the first two-thirds of gestation transfer a lower proportion of that gain to their fetus (Table 4.1). This alteration in the hierarchy of nutrient partitioning between the maternal body and her gravid uterus is independent of the protein content of the diet [82] and is unique to the adolescent growth period as it does not occur in identically treated primiparous adult ewes [83].

4.3.3 Pregnancy Outcome in Undernourished Adolescents

When adolescents are prevented from growing while pregnant the impact on pregnancy outcome is less pronounced. Accordingly in undernourished adolescents, placental weight and gestation length are equivalent to control pregnancies and no incidences of miscarriage, stillbirth or neonatal death have been recorded. By maintaining maternal body weight at conception levels, maternal nutrient reserves (mainly fat) are progressively depleted as gestation proceeds. This directly limits nutrient availability in the maternal and hence fetal circulation and leads to a slowing of fetal soft tissue growth. By late gestation and at term, the fetus is mildly growth restricted (10–17 % smaller than controls [84–86]), and using the same definition as above, only 14 % of these undernourished lambs were classified as IUGR. Furthermore, although the quantity of colostrum produced immediately after parturition was reduced it largely met the minimum requirement for IgG content and nutrient composition [86]. Thus, while both high and low dietary intakes during pregnancy negatively influence fetal growth in young adolescents, it is the overnourished model which most closely replicates the human with respect to the greater risk of miscarriage, preterm delivery, low birth weight and neonatal mortality.

4.3.4 BMI at Conception Versus Gestational Intake

The basic adolescent paradigms originally focused on manipulating dietary intake and maternal growth status immediately after pregnancy had been established and great care was taken to ensure that the adolescents were of equivalent age, weight and adiposity at conception. However, in the real world, adolescent girls have

diverse nutritional histories and enter pregnancy with varying nutrient reserves which may interact with subsequent gestational intake and growth status to influence pregnancy outcome. To partly model this scenario, two groups of adolescent ewes of the same age but with different weight and adiposity were selected 4 weeks before the application of assisted conception procedures and nutritionally managed to maintain their initial weight. In reality, this represented a 10 kg (20 %) differential in weight, and a 5 % differential in estimated body fat between groups and adolescent ewes were hence classified as having a relatively good or poor BMI at conception. Thereafter ewes were overnourished, undernourished or fed a control intake throughout gestation to drive maternal growth and gestational weight gain in contrasting directions as described previously. BMI at conception did not influence gestation length but did influence placental size and lamb birth weight (good > poor, $P < 0.001$ and $P = 0.031$, respectively). Indeed, although the initial differences in maternal weight and adiposity between groups were relatively small, ewes with a poor BMI at conception gave birth to lambs that were on average 500 g lighter than those with a good BMI. In spite of this, gestational intake still had the most marked effect on lamb birth weight (control > undernourished > overnourished, $P < 0.001$) and the percentage of lambs classified as IUGR, irrespective of baseline BMI was greatest in the overnourished group (55 % versus 4 % in control and 12.5 % in undernourished groups, $P < 0.001$ [80]).

4.3.5 Donor Ewe Adiposity Versus BMI at Conception

Pregnancy outcome may also be influenced by nutrition before conception and studies in adult sheep and rodent models report effects of varying nutrition during the pre and peri-conception periods on fetal growth and physiology [87–89]. Interpretation of these data is complex in that nutritional treatments may have carry-over effects which influence the metabolism of the dam and her early uterine environment. The assisted conception procedures used to derive the adolescent pregnancies described herein potentially offer a cleaner approach and hence the impact of maternal obesity during oocyte development and its putative interaction with nutrient reserves at conception on pregnancy outcome have been assessed. Adult donor ewes were nutritionally managed to achieve a control and obese phenotype corresponding to a 12 % differential in body fat, and these adiposity levels were maintained for 6 weeks prior to superovulation and embryo recovery. Embryos were then transferred into adolescent recipients with either a relatively good or poor BMI at conception and all were subsequently overnourished throughout gestation (2×2 factorial). A fifth group of recipients with standard BMI at conception received embryos from control donors and were fed a control intake throughout and studied in parallel: these acted as the reference point for optimal adolescent pregnancy outcome (Table 4.2). Embryo donor adiposity did not influence ovulation or embryo recovery rates, and somewhat contrary to expectation, we

Table 4.2 Impact of embryo donor adiposity during oocyte development and embryo recipient weight and adiposity at conception on pregnancy outcome in young adolescent sheep

Embryo donor adiposity	Control	Control	Obese	Obese	Two-way ANOVA *P*-value[ß]			Control*
Embryo recipient BMI	Poor	Good	Poor	Good	Donor Adiposity	Recipient BMI	Interaction	Standard
Gestational Intake	Overnourished	Overnourished	Overnourished	Overnourished				Control
Recipient wt. at ET, kg	38.2 ± 0.37^{a}	57.6 ± 0.71^{b}	38.0 ± 0.33^{a}	55.8 ± 1.01^{b}	0.141	<**0.001**	0.266	46.7 ± 0.30^{c}
[¥]Recipient adiposity at ET	2.0 ± 0.00^{a}	2.7 ± 0.02^{b}	2.0 ± 0.00^{a}	2.6 ± 0.03^{c}	**0.028**	<**0.001**	**0.028**	2.3 ± 0.01^{d}
Wt change, ET to term, kg	36.0 ± 1.27^{a}	26.9 ± 0.91^{b}	35.8 ± 1.30^{a}	25.9 ± 2.27^{b}	0.706	<**0.001**	0.781	12.7 ± 0.49^{c}
Adiposity change, ET to term	0.9 ± 0.03^{ab}	0.6 ± 0.05^{b}	1.0 ± 0.03^{a}	0.7 ± 0.11b	0.286	<**0.001**	0.801	0.1 ± 0.02^{c}
Gestation length, days	140.7 ± 0.53^{a}	141.2 ± 0.54^{a}	139.4 ± 0.59^{a}	140.6 ± 0.35^{a}	0.060	0.106	0.506	143.9 ± 0.34^{b}
Birthweight, g	3634 ± 292^{a}	4499 ± 337^{ab}	3802 ± 357^{a}	4259 ± 315^{ab}	0.912	**0.047**	0.533	5425 ± 166^{b}
[¥]Proportion IUGR	9 of 14	4 of 14	8 of 13	4 of 14	0.883	**0.035**		1 of 14
Fetal cotyledon weight, g	75 ± 9.1^{a}	107 ± 11.0^{a}	78 ± 10.6^{a}	99 ± 11.7^{a}	0.799	**0.017**	0.620	156 ± 8.2^{b}
Fetal:cotyledon weight	52 ± 3.3^{a}	44 ± 2.4^{ab}	51 ± 2.6^{a}	47 ± 3.0^{ab}	0.786	**0.036**	0.491	36 ± 1.4^{b}

Values are mean ± sem. JM Wallace, RP Aitken, JS Milne unpublished data

[ß]Four group comparison by two-way ANOVA with significant P-values in bold.

*Five group comparison analysed by one-way ANOVA (all parameters $P < 0.001$) followed post-hoc by Tukey's Method to differentiate between groups; thus, within rows values with a different superscript letter (a,b,c,d) differ at $P < 0.01$

[¥]External adiposity score determined by single experienced operator

[¥]Lambs were classified as intrauterine growth restricted (IUGR) if birthweight was < two standard deviations below the mean birthweight of the optimally nourished control group, i.e. <3939 g. Incidence of IUGR compared by binary logistic regression

Wt. weight, *ET* embryo transfer (single embryos, all from one sire)

found no evidence that embryo donor obesity (equivalent to ~33 % body fat) negatively influenced conception rate or prenatal conceptus growth following embryo transfer. The caveat is that by selecting only those oocytes that had been fertilised and developed appropriately to day 4 of the cycle, the study design avoided transferring embryos that were potentially nutritionally perturbed. Irrespective, the previously reported impact of low nutrient reserves at conception (poor BMI) on average birth weight and the incidence of IUGR was replicated here, but once again comparison with the optimally nourished control group demonstrates that high gestational intakes to promote rapid maternal growth remain the main determinant of fetal growth in young still-growing sheep.

4.3.6 Maternal Adaptations to Diverse Gestational Intakes

The endocrine responses to diverse levels of dietary intake and their putative role in nutrient partitioning during adolescent pregnancy have been extensively studied. Briefly, relative to the control group, high gestational intakes are associated with increased insulin and insulin-like growth factor 1 (IGF-1) concentrations from early in pregnancy providing a sustained anabolic stimulus to maternal tissue deposition. Metabolic challenges demonstrate that overnourished dams are insulin resistant [80] and circulating glucose levels are raised throughout gestation [90, 91]. High maternal leptin concentrations reflect that internal fat depots are elevated as early as day 50 of gestation and that maternal carcass fat content progressively increases from mid to late pregnancy [75, 92, 93]. This rapid maternal growth and increased adiposity is linked with early depletion of maternal liver iron stores during the first two-thirds of gestation and with a failure of the normal blood volume expansion of pregnancy between mid and late gestation [94]. The associated increase in maternal haematocrit, haemoglobin and plasma protein concentrations may in turn impact blood viscosity and thereby uteroplacental blood flow and fetal nutrient supply. Indeed the blood from overnourished dams at day 130 of gestation is more viscous than that of controls (1.471 ± 0.0111 units versus 1.406 ± 0.0139 units, respectively, $P < 0.001$; unpublished data).

In contrast, undernourished adolescent dams are characterised by low circulating insulin, IGF-1 and leptin concentrations: by late gestation maternal glucose concentrations are reduced and high non-esterified fatty acid concentrations reflect depleted maternal fat stores [84]. Relative blood volume expansion is unperturbed and low availability of nutrients in the maternal circulation is the main cause of the modest reduction in fetal growth velocity. This differs markedly from the situation in overnourished adolescents where in spite of excess nutrients in the maternal circulation, fetal growth restriction is mediated by major alterations in placental growth and function.

4.3.7 Placental Adaptations to Diverse Gestational Intakes

While cross-sectional studies at key stages of development demonstrate that placental mass is not significantly perturbed until the beginning of the final third of gestation [95], the adaptations that underlie the placental programming of fetal growth restriction in overnourished adolescents can be detected from early in pregnancy. Accordingly, reduced proliferative activity was measured in both placental compartments at day 50 of pregnancy [96], and, in a separate study at the same stage, vascular development (i.e. vessel size) within the fetal cotyledon was already impaired [93]. In addition, there was a delay in the onset and magnitude of placental lactogen and pregnancy-specific protein-B concentrations indicative of reduced trophoblast cell migration [76, 81] and by the beginning of the second third of gestation placental steroid secretion was lower than in control-fed dams [76, 77, 97]. At mid-pregnancy and the apex of placental growth, angiogenic growth factor ligand and receptor mRNA expression was attenuated and indices of proliferation and apoptosis perturbed [98, 99]. These adaptations preceded the change in placental mass and together indicate that the placentae were already on a different developmental and haemodynamic trajectory. In support, uterine blood flow was reduced and umbilical artery Doppler indices increased in overnourished pregnancies at mid-gestation and both predicted the reduced fetal growth velocity observed during the final third of gestation [100, 101]. By late gestation (~day 133) placental weight was ~45 % lower, and similarly uterine and umbilical blood flows, uteroplacental glucose and oxygen consumption and lactate production, and placental glucose transport were all reduced by 35–40 % relative to control pregnancies. However, all the aforementioned parameters were equivalent between groups when expressed on a placental and or fetal weight-specific basis [102, 103], indicating that it is the small size of the placenta rather than altered nutrient uptake, metabolism and transport which mediates reduced fetal growth velocity in the final third of gestation in these rapidly growing adolescents.

Initial nutritional switch-over studies indicated that the placental growth trajectory could be rescued by reducing maternal intakes from a high to a control level at day 50 of gestation, thereby restoring birth weight to the same level as in dams fed control rations throughout. In contrast an abrupt increase in dietary intake at this time inhibited placental and fetal growth to the same degree as in continuously overnourished dams [91]. In a more recent study when the dietary intake of overnourished dams was radically reduced sufficient to induce major maternal catabolism during the final third of pregnancy (high to low intake from day 90–130, HL), placental expression of five angiogenic genes including vascular endothelial growth factor (VEGF) was upregulated in the fetal cotyledon. This is commensurate with blood vessel remodelling, but in spite of this presumed adaptation, placental mass and fetal weight could not be rescued and were equivalent in high versus HL groups [104]. Thus, unsurprisingly the placenta is most sensitive to abrupt changes in maternal nutrition during its main proliferative growth phase.

The precise mechanisms underlying the nutritionally induced suppression of placental growth have however remained elusive. Attempts to reverse the negative effects of overfeeding by restoring circulating maternal oestrogen or progesterone concentrations to control levels during early-mid gestation have failed to influence placental vascularity or rescue placental weight as assessed at late gestation or at term, respectively [97, 105]. In contrast overnourished pregnancies are also characterised by attenuated growth hormone (GH) secretion and when dams were treated with exogenous GH during the period of rapid placental proliferation (day 35–80) an initial study indicated nutrient partitioning was altered in favour of uteroplacental and fetal growth as assessed at day 81 of gestation [106]. In a subsequent study, maternal GH treatment either targeted the period of rapid placental growth or the period after placental growth was complete and fetal nutrient demand was high. These early (day 35–65) and late (day 95–125) pregnancy GH treatments both had a major influence on maternal metabolism, resulting in insulin resistance, decreased lipogenesis and a threefold increase in maternal glucose concentrations. For the late pregnancy group this resulted in a modest stimulation of fetal growth and a major increase in fetal adiposity at day 130 of gestation which was independent of any change in placenta size, suggesting that while GH has a major impact on nutrient partitioning within the still-maturing somatotrophic axis of the pregnant adolescent it does not act directly on the placenta [107].

In undernourished adolescents neither placental proliferation nor mass differed from control pregnancies at mid-late gestation or following spontaneous delivery at term [85, 86]. Irrespective, vascular changes within the placenta may play a role in mediating the reduction in nutrient supply between the dam and her fetus in these pregnancies. A robust 20 % decrease in capillary area density within the maternal caruncular component of the placenta was measured at both day 90 and 130 of gestation and could not be reversed by re-alimentation to control intakes between these two stages [85]. Contemporaneous assessments of uterine blood flow (UtBF) in vivo in undernourished compared with control dams suggest that the reduction in capillary development is mirrored by a decrease in average flow of similar magnitude [average daily UtBF between day 88 and 135 of gestation $= 418 \pm 43$ and 326 ± 23 ml/min in control ($n = 9$) and undernourished ($n = 11$) pregnancies, respectively, $P = 0.08$]. This modest reduction in uterine blood flow may in part be secondary to mild maternal anaemia as low intakes are associated with a decrease in maternal haematocrit and haemoglobin content relative to control dams by late gestation (30 ± 0.4 % versus 35 ± 0.6 % and 9.6 ± 0.13 g/dl versus 10.6 ± 0.17 g/dl, $n = 21$ and 16 per group respectively, $P < 0.001$; unpublished).

There is a paucity of placental data in relation to growth and nutrition in human adolescents. Path analysis in a large cohort of Peruvian women suggests that the contribution of placental weight to birth weight was less in girls who were still growing [70], and similarly umbilical artery Doppler indices were elevated indicating reduced flow in growers versus non-growers in the Camden Study [67]. In contrast, in more contemporary studies, placental weight and morphometry were independent of adolescent growth status, but adolescents per se had inherently reduced placental transport of amino acids compared with adults [108, 109]. Unlike

in our sheep paradigms, it is important to emphasise that non-growers may comprise girls who are skeletally mature and those whose growth is constrained by poor nutrient intakes making the data complex to interpret.

4.3.8 Fetal Consequences of Diverse Gestational Intakes

Regular ultrasound examination allows fetal growth velocity to be monitored non-invasively throughout gestation and accordingly in the overnourished adolescents various indices of fetal size including abdominal circumference (AC), renal volume (RV) and femur and tibia lengths were reduced from around day 100 of gestation onwards compared with normally growing control fetuses [101]. This relatively late-onset fetal growth restriction is asymmetric in that growth of the brain and adrenal glands were preserved at the expense of the visceral organs [102, 110, 111]. The access to the placental and fetal circulation offered in sheep models additionally allows interrogation of fetal endocrine and nutrient status, nutrient uptakes and metabolism. So in late gestation the growth-restricted fetuses are characterised by absolute reductions in umbilical (fetal) uptakes of glucose, oxygen and amino acids which are equivalent to normally growing control fetuses when expressed on a fetal weight-specific basis [75, 102, 103, 111]. Moreover, even though the growth-restricted fetus increases glucose extraction in an attempt to offset diminished glucose supply, the concentrations of glucose, insulin and IGF-1 in the fetal circulation remain low. The fetal sensitivity to insulin and glucose has been examined during fetal hyperinsulinaemic–euglycaemic and hyperglycaemic–euinsulinaemic clamps and reveals normal body weight-specific responses to short-term experimental increases in plasma insulin and/or glucose [112]. This is indicative of maintained mechanisms of insulin action and glucose uptake/utilisation capacity allowing the fetus to preserve essential metabolic functions at the expense of body growth. If such adaptations persist, these IUGR offspring may be vulnerable to increased fat deposition postnatally when nutrient supply is no longer limiting. Indeed, there are indications that the growth-restricted fetuses of overnourished dams may already have a relatively fat phenotype prior to birth. Thus, while absolute perirenal adipose tissue (PAT) mass is reduced, fetal weight-specific PAT mass and carcass fat content are greater [113] and plasma cholesterol and LDL levels at birth are elevated [86]. This increase in relative adiposity may have its origins earlier in gestation prior to placental limitation of absolute fetal glucose supply. Thus, greater glucose concentrations in the amniotic fluid at day 50 and in the fetal plasma at both day 77 and 90 of gestation [93] may drive an increase in adipocyte proliferation in early-mid pregnancy and thereby increased potential for fat accumulation in late pregnancy and beyond. While definitive evidence to support such a hypothesis is lacking, it is noteworthy that appetite regulatory genes in the fetal hypothalamus (primarily anorexigenic neuropeptides) are responsive to fetal hyperglycaemia at mid and late gestation [114, 115]. Furthermore, relative to normal birthweight controls, both male and female IUGR offspring

of overnourished dams display rapid fractional growth rates particularly during the neonatal period, have more body fat at weaning at 3 months of age and show altered metabolic responses to exogenous glucose from juvenile through to adult life [116].

In direct contrast, fetuses of undernourished adolescent dams have a thin phenotype. Key genes that regulate fetal adipocyte proliferation and function are active at mid-gestation when they are sensitive to maternal undernutrition: this leads to reduced fetal adiposity by late pregnancy while skeletal growth is preserved [117]. In this instance, the fetal hypothalamus is sensitive to presumed fetal hypoglycaemia and orexigenic neuropeptides are upregulated in the fetuses of undernourished dams. Crucially the expression of these genes can be normalised by realimenting undernourished dams to a control intake between mid and late pregnancy [118]. At birth, plasma lipids in the modestly growth-restricted offspring are equivalent to normally growing controls and thereafter there is little evidence of altered growth, perturbed metabolism or body composition [86].

4.3.9 Translational Perspectives

Essential differences between these ruminant-based experimental studies and human pregnancies are fully appreciated. Nevertheless, the information obtained from these highly controlled paradigms has implications for both young adolescents and for women at risk of adverse pregnancy outcome irrespective of maternal age. For young adolescent girls, it is clear that both nutrient reserves at conception and gestational dietary intake thereafter are likely to be a powerful determinant of fetal growth particularly if maternal growth per se is ongoing or incomplete. In cultures where early marriage soon after menarche and hence pregnancy during young adolescent life is normal, girls with a low BMI should be encouraged to gain weight and achieve a normal BMI before conception. Thereafter, dietary intakes should be sufficient to maintain maternal nutrient reserves throughout gestation and meet fetal nutrient requirements particularly during the rapid growth phase in the final third of gestation. Measuring changes in skinfold thickness in addition to monitoring weight gain may be a simple and beneficial tool in this respect. Determining the growth status of individual adolescents at pregnancy outset is likely to be challenging, and while measuring, biomarkers of growth and nutrient status may be helpful in predicting the risk of poor outcomes, studies verifying such an approach are currently lacking. Where adolescent pregnancies are unplanned and calorie intakes likely to be high, the mother should be advised of the dangers of overeating and excessive weight gain during pregnancy, particularly during the period spanning placental proliferation. Indeed, as the placenta is central to mediating poor pregnancy outcome in young adolescents, early diagnosis of deficiencies in uteroplacental growth and/or blood flow is likely to be beneficial for identifying those at risk of fetal growth restriction.

Similarly for pregnant women irrespective of age, placental size plays a pivotal role in determining the fetal growth trajectory and birthweight extremes. Recent analysis of pregnancy complication risk reveals that placental weight in the lower tertile for a given population is a risk factor for pre-eclampsia, spontaneous preterm delivery, stillbirth and low birthweight while a placental weight in the upper tertile is associated with a higher risk of caesarean section and high birthweight [119]. Placental weight increases with increasing maternal BMI at conception through underweight to morbidly obese categories (4 g per BMI unit), and relative to women with a normal BMI, underweight women are more likely to experience placental growth restriction, while obese women have a twofold higher risk of having a large placenta: thus, the growth and final size of the placenta offers an explanation for the aforementioned relationship between the extremes of maternal BMI and pregnancy outcome. In addition, the placenta is sensitive to changes in maternal weight between consecutive pregnancies and appears to lie on the causal pathway between both inter-pregnancy BMI loss and BMI gain leading to a greater risk of SGA and LGA, respectively, at the second delivery [120]. The implication is that weight change between pregnancies impacts maternal nutrient reserves at the start of the second pregnancy and hence the placental growth trajectory as shown in the aforesaid sheep studies. Again placental screening in the first trimester may help early identification and appropriate management of those at risk [121].

Finally, as uteroplacental insufficiency and low uterine blood flow are the main underlying cause of most severe fetal growth restriction, there is a requirement to develop therapies to improve fetal nutrient supply, maintain growth and extend gestation until the baby can be delivered safely and survive without handicap. A potential therapy involving local uterine artery adenovirus (Ad.)-mediated overexpression of vascular endothelial growth factor (VEGF) in the putatively growth-restricted pregnancies of overnourished adolescent dams has been evaluated. Ad.VEGF administration in mid-pregnancy robustly increased fetal growth velocity as measured at 3 and 4 weeks after treatment, reduced the incidence of IUGR and increased birth weight by 20 % [122]. Proof of concept that this gene therapy is safe and efficacious in sheep now paves the way for clinical trials.

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