Grundlagenreferate

Diet, Exercise, and Feto-placental Growth

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Abstract

Background and Objective: Evidence from multiple sources indicates that maternal blood glucose levels correlate directly with size at birth and that both diet and exercise alter them. The purpose of these preliminary studies was to test the hypothesis that the carbohydrate mix in a pregnant woman's diet modifies the primary effect of exercise on feto-placental growth through its effects on maternal blood glucose levels.
Experimental Designs and Methods: A prospective randomized design was used to examine the effects of two isocaloric, high carbohydrate diets combined with regular exercise on maternal blood glucose levels and various indices of morphometric outcome in healthy pregnant women (n = 12). The diets differed only in the type of carbohydrate ingested. Those in one had low glycemic indices and those in the other had high glycemic indices.
Results: During pregnancy, women on the low glycemic carbohydrate diet experienced no significant change in their glycemic response to mixed caloric intake while those who switched to the high glycemic carbohydrate diet experienced a 190 % increase in their response. The later was associated with larger placental size, increased birth weight, and greater maternal weight gain.
Conclusion: These preliminary data indicate that the type of dietary carbohydrate in a physically active pregnant woman's diet influences her blood glucose profile which alters placental growth, size at birth, and weight gain.

Introduction

For many years people thought that what a woman ate and what she did physically during pregnancy should have an impact on fetal growth. This opinion stimulated investigators to gather a large amount of data in humans during times of famine, natural disasters, and food supplementation programs. The data they obtained did not support the initial thought. Rather it indicated that the amount of calories ingested had little if any effect on size at birth over a wide range of intakes and lev-

els of physical activity. However, more recent findings suggest that the type rather than the total number of calories and the type rather than the absolute amount of physical activity do make a real difference in the rate of feto-placental growth [1-6].

It has been recognized for some time that maternal 24 hour blood glucose levels in late gestation correlate directly with fetal growth rate and size at birth in both the sheep and man and the same is true for uterine and/or placental bed blood flow [4, 7–12]. For example, restricting a pregnant ewe's caloric intake lowers her blood sugar which is accompanied by an immediate decrease in fetal growth rate, the same occurs when mechanical methods are used to chronically reduce uterine blood flow, and similar findings are observed in human pregnancies complicated by hypoglycemia or postural hypotension. Studies like these support the general conclusion that one of the primary environmental factors which regulate feto-placental growth is the rate of substrate delivery to the placenta which is calculated as the product of the rate of blood flow and the substrate concentration. Thus, factors which change either the rate of blood flow or maternal blood levels of something like glucose should alter the rate of fetal growth.

Additional experiments in both the sheep and guinea pig reviewed elsewhere [4], indicate that this direct relationship between substrate availability and feto-placental growth rate is quite sensitive, rapidly responsive, and locally regulated by changes in the placental release of growth suppressive peptides into the feto-placental circulation. Again, the initial stimulus appears to be a change in maternal substrate delivery. When it increases, the release of these peptides from the placenta decreases and when it decreases placental release increases. Thus, this simple regulatory mechanism is based on the law of supply and demand. As such, it clearly has fetal survival value and probably is the major reason why the normal range in birth weight is so wide.

This regulatory mechanism can also explain why many factors which are part of a woman's everyday life influence fetal growth and size at birth and initially it seemed to me that it explained the decreased birth weights seen in the offspring of exercising women [5, 6]. Women who continued, regular, moderate to high intensity, weight-bearing exercise throughout pregnancy delivered lean infants who weighed about 300 gm less than matched controls. As this type of exercise during pregnancy decreased both maternal blood glucose and blood flow to the uterus [5, 6, 13–16], it appeared that the difference in birth weight and neonatal fat mass was simply a normal response to the exercised-induced reduction in glucose delivery which increased the placental release of growth suppressive peptides and slowed growth. However, this alone could not explain why wide differences (as much as 600 gm) in birth weight were observed in the infants born of women who had performed approximately the same amounts of exercise during pregnancy.

In an attempt to explain this discrepancy, we focused on dietary carbohydrate because multiple nutritional studies and observations indicated that both the type and amount of carbohydrate in the diet influence blood glucose levels [1–4, 15–19]. In addition, most women who exercise eat a high carbohydrate diet and, as there is a direct relationship between maternal blood glucose levels and size at birth, it appeared likely that dietary carbohydrate might well explain the discrepant birth weight seen in the offspring of some exercising women. This lead to an initial series of dietary intervention studies in nonpregnant women which demonstrated that

varying the type of carbohydrates in the diet from those with low glycemic indices to those with high glycemic indices increased the postprandial blood glucose response by approximately 100 % [20]. These findings led to the current study which was designed to test the hypothesis that similar differences in the carbohydrate mix in a pregnant woman's diet modify the primary effect of exercise on feto-placental growth through their effects on maternal blood glucose levels. This report focuses on the morphometric outcomes observed in the initial 12 subjects. The dietary effects on maternal blood glucose levels were similar to those observed in nonpregnant women and have been reported in detail elsewhere [20].

Experimental Design and Methods

Protocol design: The experimental protocol is prospective and dietary assignment is randomized. To date 12 healthy women have enrolled and completed an uncomplicated pregnancy. All gave informed consent and the protocol was approved by the Hospital Ethics Committee. They were enrolled prior to pregnancy and placed on a regular regimen of supervised exercise consisting of 20 minutes of weight-bearing exercise 3 times a week at an intensity equal to 55 % of each individual's maximum capacity ($VO2_{max}$). They also began a weight maintaining diet which contained 55–60 % of its calories as carbohydrate derived from sources with predominantly low glycemic indices. All continued the same exercise regimen throughout pregnancy but at 8 weeks gestation, they were randomized to either continue the preconceptional diet containing carbohydrates derived from low glycemic sources (n = 6), or were switched to an isocaloric diet containing similar quantities of protein, fat, and carbohydrate whose carbohydrates were derived from high glycemic sources (n = 6). Serial measurements of weight, skinfold thicknesses and midtrimester placental growth were obtained during pregnancy and, at delivery, detailed morphometric measurements of the placenta and newborn infant were performed using carefully standardized techniques.

Table 1. Sample Diets

Aboriginal Carbohydrate Diet	Cafeteria Carbohydrate Diet
Breakfast All bran cereal, skim milk, grapefruit	*Breakfast* Rice chex, skim milk, ripe banana/mango
Lunch Turkey breast, whole grain bread, mayonnaise, low fat fruit yogurt	*Lunch* Turkey breast, Kaiser roll, mayonnaise, corn chips or potato chips
Dinner Roast chicken, fettucini, margarine, green peas, low fat ice cream	*Dinner* Roast chicken, baked potato, margarine, carrots, angel food cake
Snacks Peanuts, apples, oranges, chocolate	*Snacks* Graham crackers, candy bar, coke

The two diets: Both diets were designed to contain 17–19 % protein 20–25 % fat and 55–60 % carbohydrate. Total caloric content was based on fat free mass and weight stability in the nonpregnant state (35–45 kcal/kg lean body mass/day). During pregnancy all women were allowed to increase caloric intake according to appetite with advancing gestation. The diet containing carbohydrates with high glycemic indices used carbohydrate products which came from highly processed grains, root vegetables, and simple sugars whereas the diet containing the carbohydrates with low glycemic indices used carbohydrate products made from unprocessed whole grains, fruits, beans, vegetables and many dairy products. The former includes many highly refined breads, potatoes, instant rice, most breakfast cereals, deserts, and snack type foods (so-called "cafeteria" type carbohydrate). The latter include most dense whole grain and multi grain breads, bran cereals, pastas, fresh fruits and vegetables, yogurt, ice cream and nuts (so-called "aboriginal" type carbohydrate). Dietary compliance was assessed by 24 hour dietary recalls obtained at random times twice each week. Caloric intake, diet composition, the glycemic indices of the carbohydrate portion of the diet, and the overall dietary glycemic index were calculated using a standardized approach [20–22]. A typical day's diet for each group is illustrated in table 1.

Additional methodology: Shortly after enrollment each woman underwent a fitness assessment which included height, weight in light exercise gear, measurement of 5 site skinfold thicknesses with Harpenden calipers [23], and a constant speed, progressive grade treadmill test to determine $VO2_{max}$ [24]. The latter value was used to normalize exercise intensity between the subjects at 55 % of $VO2_{max}$ and the sum of the 5 skinfold thicknesses were used to estimate % body fat and lean body mass using equations developed in a similar populace using hydro densitometry [25]. Measurements of weight and height were repeated each lunar month throughout pregnancy. Placental volume was measured in the 16th, 20th, and 24th week of gestation using B-mode ultrasound and a trimmed, drained placental weight was obtained in a standardized fashion at the time of delivery [26]. Neonatal measurements were obtained within 24 hours of birth and measures of fat mass were repeated at 5 days of age. Birth weight was measured to the nearest 10 gm and length to the nearest mm using a specially constructed measurement box [27]. Circumferential measures were obtained with a cloth tape to the nearest mm in mid-inspiration with the infant quiet, and neonatal fat mass was estimated using both skinfold thicknesses and total body electrical conductivity [28]. Statistically significant between group differences were detected using analysis of variance. The data are expressed as the mean ± s.e.m. and significance was set at the 0.05 level.

Results

Subject characteristics and blood glucose responses: These data have been detailed in an earlier report [20]. Briefly, at the time of entry, the 6 women eventually randomized to each of the dietary regimens were similar in age (35 ± 1 versus 34 ± 1 years), preconceptional weight (62.0 ± 2.1 versus 62.5 ± 3.1 kg), % body fat (20.7 ± 1.9 versus 20.5 ± 1.9, and parity (0–1 versus 0–3). Two subjects in each group ex-

Table 2. Neonatal Morphometrics

Parameters	Aboriginal Carbohydrate Diet	Cafeteria Carbohydrate Diet
Birthweight (kg)	3.27 ± 0.12	4.25 ± 0.11*
Length (cm)	50.3 ± 0.7	53.1 ± 0.5*
Head circumference (cm)	34.6 ± 0.3	36.6 ± 0.7*
Abd. circumference (cm)	29.9 ± 0.3	32.4 ± 0.4*
% Body fat	9.4 ± 1.5	11.1 ± 1.9
Fat mass (gm)	301 ± 51	402 ± 80*
Lean body mass (kg)	2.98 ± 0.09	3.84 ± 0.09*

Data presented as the mean ± s.e.m., * = $p < 0.01$, Abd. = abdominal

ercised regularly at the time of enrollment and all save one were totally compliant with the prescribed exercise regimen throughout pregnancy. The single exception performed approximately 3 times more exercise than prescribed.

Dietary compliance was equal in the two groups with average daily caloric intakes and % dietary carbohydrate of 47 ± 3 versus 44 ± 2 Kcal/kg/day and 59 ± 3 versus 56 ± 2 % in the groups who ate the cafeteria and aboriginal type of carbohydrates respectively. However, their average glycemic indices differed significantly ($p < 0.001$), being 84 ± 1 on the cafeteria carbohydrate diet and 71 ± 1 on the aboriginal carbohydrate diet. In addition, both the response pattern and the area under their 3 hour postprandial glucose curves differed significantly in mid and late gestation averaging approximately 15 mg/min higher in the women whose diets contained the cafeteria types of carbohydrates and similar trends were seen in the blood glucose response to exercise in the two groups [20].

Placental growth: The rate at which placental volume increased between the 16th and 24th week of gestation was significantly different ($p < 0.01$) between the two diet groups. The placental volumes of the women who ate the diet containing aboriginal types of carbohydrates increased at an average rate of 19 ± 4 cc/week whereas those of the women who ate the diet containing cafeteria types of carbohydrate increased more than a third faster (34 ± 5 cc/week), over the same time interval. As a result there was a marked difference in absolute volume in the 24th week (248 ± 25 versus 411 ± 30 cc, $p < 0.001$) and, at the time of delivery, a similar difference ($p < 0.001$) in the weight of placental tissue (after removal of the membranes, clots, and expressible blood) was observed. The placentae delivered of the women whose diets contained aboriginal types of carbohydrates weighed 396 ± 18 gram while those from the women whose diets contained cafeteria types of carbohydrate weighed 575 ± 52 gram.

Neonatal morphometrics: The neonatal measurements obtained in the two groups are detailed in Table 2. Note that the morphometric measures in the 6 infants born of the women whose diets contained aboriginal types of carbohydrates were average, most being between the 40th and 50th percentile when compared to normative

values for healthy term neonates. The one exception was body fat which ranged between the 10th and 35th percentile. In contrast, the morphometric measures in the 6 offspring of the women who ate cafeteria types of carbohydrates indicated that they were symmetrically overgrown with all parameters other than body fat at or above the 90th percentile. However, neither measure of body fat was significantly different from that obtained in the offspring of the aboriginal carbohydrate group.

Maternal morphometrics: To date, despite equivalent caloric intakes, the women in the two dietary groups have experienced significantly different ($p < 0.01$) pregnancy weight gain. The 6 women whose diet contained the aboriginal types of carbohydrates had an overall weight gain of 11.8 ± 2.3 kg while overall weight gain in those whose diet contained cafeteria types of carbohydrates was 19.7 ± 1.2 kg. The increase in the Σ of the skinfold thicknesses at 5 sites followed a similar pattern (14.4 ± 2.2 versus 27.8 ± 3.1 mm) suggesting that a moderate amount of the difference in weight gain was do to a significant difference in maternal fat deposition and/or retention.

Discussion

This study was undertaken to examine the possibility that dietary induced differences in maternal blood glucose levels modify the effects of regular exercise on feto-placental growth and the preliminary data for these initial 12 subjects suggests that this is indeed the case. Compliance has been excellent and the differences in morphometric outcome on the two diets has been wide so it is unlikely that a larger sample size will substantially alter the results obtained to date.

These results support both the idea that substrate delivery to the placental site is a major determinant of feto-placental growth and the existence of a placental regulatory mechanism which is responsive to changes in substrate delivery. Indeed, the differences in birth weight are similar to those observed by Langer et al. in women who have been treated for minor abnormalities in blood glucose levels in late gestation [8, 9]. They found that a difference in maternal blood sugar level of 15 to 20 mg/dl had a dramatic effect on the incidence of small for gestational age and large for gestational age infants. However, there is one major difference. The offspring of the gestation diabetic characteristically have a large increase in fat mass. In the current series, this was not the case in the offspring of the women whose diet contained cafeteria types of carbohydrate. Although they were overgrown, the overgrowth was symmetrical and their % body fat was well within the normal range. This probably reflects the effect of exercise on fetal fat deposition in late pregnancy [4–6].

These findings support earlier work indicating that the addition of regular exercise to the usual dietary regimen in gestational diabetes may help to reduce maternal blood sugar and avoid the necessity for insulin therapy [15, 16]. In addition, they suggest that the limiting dietary carbohydrates to those of the aboriginal type may offer an additional advantage. Finally, they suggest that the addition of cafeteria types of carbohydrate to the diet may have preventative and/or therapeutic value in cases at risk for intrauterine growth retardation [4]. Clearly randomized clinical trials will be necessary to determine if either is the case.

The magnitude of the difference in overall energy retention in the form of new tissue (mother, fetus, and placenta) on the two diets was quite unanticipated. As there were no large differences in caloric intake between the two groups, it suggests that the amount and type of carbohydrate in the diet may also influence one or more aspects of energy expenditure (resting metabolic rate, dietary induced thermogenesis, or physical efficiency). Experiments are currently being designed to assess each of these possibilities.

Conclusions

These preliminary results indicate that type of dietary carbohydrate in a healthy, physically active woman's diet influences weight gain, placental growth, and size at birth. They support the idea that substrate availability is a major determinant of feto-placental growth and suggest that exercise combined with an alteration in dietary carbohydrate intake may have a preventative and/or therapeutic role in a variety of clinical situations.

Acknowledgment

The author would also like to acknowledge the dedication of Ms. Susan Ridzon, R. D. whose attention to detail was essential to the protocol's success.

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Prostaglandins and Parturition

J. R. G. Challis

Introduction

The regulation of myometrial contractility and uterine responsiveness during pregnancy can be considered in different phases ([1]; Fig. 1). For much of pregnancy (Phase 0) the myometrium is in a state of relative quiescence. It is acted upon by inhibitors that may include progesterone, prostacyclin, relaxin, parathyroid hormone related peptide and nitric oxide. It is evident that withdrawal of the action of one or more of these compounds from the myometrium may occur in relationship to labor at term. It is also apparent that premature withdrawal of one or more of these compounds from the myometrium could predispose to premature delivery. Uterine contractility at term can be considered in two stages; activation (Phase 1) and stimulation (Phase 2). During activation the myometrium is influenced by uterotrophins, amongst which it is presumed that estrogen has a dominant role. Estrogen increases the expression of contraction-associated proteins (CAPS). These include connexin-43, the major protein comprising gap junctions between myocytes during labor, receptors for oxytocin and prostaglandins, and changes leading to increased functional activity of ion channels. With activation, the uterus can then be stimulated by the action of uterotonins, amongst which oxytocin and prostaglandins are believed to have a predominant role [2].

It is meaningful to ask two critical questions: *First*; Are prostaglandins initiators of parturition? Clearly, the answer is no. The initiation of parturition can be considered at the latest during the switch from quiescence to activation (Phase 0 to Phase 1), and probably much earlier. *Second*; Are prostaglandins obligatory for parturition? Again, the answer is likely no. Lessons from experiments with gene null mutations and transgenesis in a variety of systems have indicated the existence of backup and alternative processes. Prostaglandin synthase Type II knock-out mice have reduced fertility and have not been studied in relation to gestation length [3]. Prostaglandin synthase Type 1 knock-out mice may have protracted labor, and do deliver, although the young have poor viability [4]. The best indications for an important role of prostaglandins in the parturitional process include evidence for increased PG production prior to the appearance of labor-like myometrial contractility, and the effects of PGHS inhibitors such as indomethacin in suppressing myometrial contractility and prolonging the length of gestation [5].

Prostaglandin synthesis and metabolism

Primary prostaglandins are formed from unesterified arachidonic acid, derived in turn from membrane phospholipids (Fig. 2). Free arachidonic acid is liberated through the activities of one or more isozymes of phospholipase C, or of forms of phospholipase A_2. Cytosolic PLA_2 ($cPLA_2$) is an 84 kDalton protein, and levels of its mRNA increase in placental tissue taken from patients in late gestation. Secre-

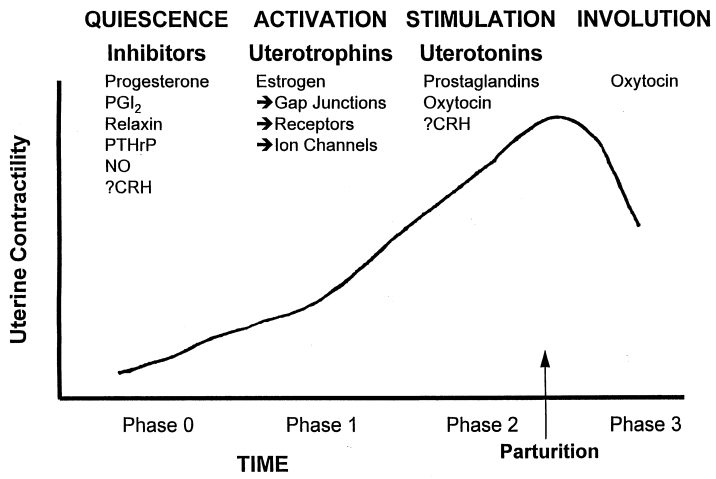

Fig. 1. Relationship between regulators of myometrial contractility, patterns of uterine contractility and time in relation to the onset of parturition. PGI_2, prostacyclin; PTHrP, parathyroid hormone-related peptide; NO, nitric oxide; CRH, corticotrophin-releasing hormone

tory PLA_2 ($sPLA_2$) is a 14 kDalton protein that is produced and secreted by trophoblast, and then acts through extra-cellular receptors. Free arachidonic acid is converted to PGG_2/PGH_2, which are intermediate in the formation of PGE_2, $PGF_{2\alpha}$, thromboxane and prostacyclin. Formation of PGH_2 is catalyzed by PGH-synthase (PGHS) which is rate-limiting in the regulation of prostaglandin formation in a number of systems.

Two forms of PGHS have now been identified, cloned and characterized. Both are heme proteins composed of two 70 kDa subunits, and containing both cyclooxygenase and peroxidase activities. Non-steroidal anti-inflammatory drugs (NSAIDs) act through inhibition of the cyclooxygenase activity of PGHS. Regulation of PGHS transcription and translation is important in many cell systems. The constitutive form of PGHS (PGHS-1) has been purified, characterized, and cloned from mouse, ram and human. Regulation of PGHS-1 expression can occur in some cell types, and the term "constitutive" may be misleading in this sense. PGHS-2 has been cloned from several species including human, mouse, rat and chicken. It has considerable homology with PGHS-1, but contains a unique 17 amino acid residue C-terminal segment. cDNA's for the two PGHS isoforms have approximately 60–65% homology. In many cell types glucocorticoids suppress expression of PGHS-2, whereas this gene is upregulated by cytokines and growth factors. NSAID's differ in their Ki values of PGHS-1 and PGHS-2. For reasons that will become apparent, development of NSAID's that preferentially inhibit PGHS-2 may be of particular value in the management of preterm labor.

Arachidonic acid may also be metabolized through one of at least four distinct lipoxygenase pathways. These include 5-lipoxygenase, leukocyte-type 12-lipoxygenase, platelet-type 12-lipoxygenase and 15-lipoxygenase. Arachidonic acid is converted through 5 lipoxygenase to form 5-H(P)ETE, which can be converted

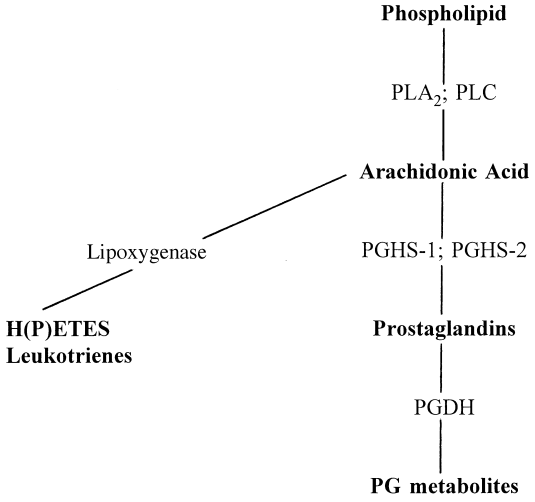

Fig. 2. Pathways of arachidonic acid metabolism. PLA_2, phospholipase A_2; PLC, phospholipase C; PGHS-1, prostaglandin synthase-1; PGHS-2, prostaglandin synthase-2; PGDH, 15-hydroxyprostaglandin dehydrogenase

to leukotriene A_4 (LTA_4), which in turn may by hydrolyzed into LTB_4 or LTC_4. 12- and 15-lipoxygenase activities result in formation from arachidonic acid of 12-H(P)ETE and 15-H(P)ETE. Production of these compounds may be elevated at labor and preterm labor, and they can affect contractility of smooth muscle. However, regulation of these lipoxygenase enzymes has been studied much less that PGHS.

The major metabolizing enzymes for PG's include an NAD^+ dependent 15-hydroxyprostaglandin dehydrogenase (PGDH) which catalyzes oxidation of the 15-OH group of PG's of the E and F series. The initial step in PG metabolism results in formation of 15-keto and 13, 14-dihydro 15-keto metabolites, which have reduced biological activity. This step may be important in preventing biologically active prostaglandins derived from amnion and/or chorion from reaching decidua and myometrium through most of pregnancy. The failure of this inactivation may be one cause of preterm delivery.

Prostaglandins act through specific receptors including the four main sub-types, EP_1, EP_2, EP_3 and EP_4 for PGE_2 and FP receptors for $PGF_{2\alpha}$ [7]. EP_1 and EP_3 receptors mediate contractions of smooth muscle in the number of tissues through mechanisms that include calcium mobilization and inhibition of intracellular cyclic AMP. EP_3 receptors exist as a number of isoforms produced following alternative RNA splicing of a single gene product. EP_2 and EP_4 receptors act through increased cAMP formation and relax smooth muscle. Expression of EP_1, EP_3, EP_4 and FP receptors in the human myometrium and fetal membranes has been established (Teoh and Lye, unpublished) during pregnancy. Information is now urgently required on the distribution and possible differential regulation of these different receptor subtypes in human fetal membranes and intrauterine tissues with the onset of labor.

Prostaglandins and ovine parturition

Parturition is initiated in animals such as sheep by the fetus, through activation of the fetal hypothalamic-pituitary-adrenal axis [8]. Fetal plasma cortisol concentrations rise in late gestation and precede a decrease in the output of progesterone, and an increase in the output of estrogen from the placenta. It has been suggested that fetal glucocorticoids trigger these changes through activation in the placenta of the enzyme $P450_{C17}$, thereby allowing placental metabolism of C_{21} steroids completely through to estrogen [9, 10]. The changes in steroid output are accompanied by an increase in the concentrations of $PGF_{2\alpha}$, measurable in the maternal utero-ovarian venous blood, during the last 12–24 h before delivery occurs [11]. In the fetal circulation, however, PGE_2 is the principal PG, and its concentration increases progressively over the last 15–20 days of gestation [12]. The difference in profiles of PGE_2 and $PGF_{2\alpha}$ in the fetal and maternal circulation raises the possibility that these may be derived from different tissues. PGE_2 in the fetal circulation may be derived predominantly from placental trophoblast (fetal tissue), whereas $PGF_{2\alpha}$, in the maternal circulation, may be derived predominantly from endometrium and myometrium (maternal tissues).

Metabolism of arachidonic acid occurs through both prostaglandin synthase and lipoxygenase pathways in amnion, chorion and placenta from as early as day 50 of gestation [13]. The rate of arachidonic acid metabolism by amnion exceeds that in chorion and placenta at days 50, 100 and 125 (term = 145 days). At term, however, metabolism of arachidonic acid by placental tissue increases. Further, arachidonic acid is now processed preferentially through the PGHS rather than through the lipoxygenase pathway. A similar, directed pathway of arachidonate metabolism has been reported in human amnion obtained at the time of labor [14]. The increase in PGHS activity and PGHS protein in sheep placenta with advancing gestation is due to increased expression of PGHS-2 mRNA. Using immunohistochemistry and *in situ* hybridization, PGHS-2 localizes to the trophoblast component of placenta and PGHS-2 mRNA levels and PGHS immunoreactivity increase with advancing gestation. There was no change in PGHS-1 mRNA in placenta over this period of time. Levels of PGHS-2 mRNA but not PGHS-1 mRNA were elevated in maternal endometrium and myometrium during the progression of labor, both at term and after the administration of glucocorticoid to fetal sheep. We (Gibb and Challis, unpublished) have found that PGHS-2 localizes predominantly to the luminal epithelium in the endometrium and to myocytes in myometrium, whereas PGHS-1 mRNA was detectable only in myometrium.

After infusion of glucocorticoid to the fetal lamb *in utero* there is an increase in PGHS activity in the placenta [13], and in PGHS-2, but not PGHS-1 mRNA in placental trophoblast (Jeffray, Gibb & Challis, unpublished). Current studies suggest that this is not mediated by the rise in estrogen, although estrogen can increase levels of PGHS-2 mRNA in myometrium and endometrium (maternal tissues) from non-pregnant sheep [16]. Previously, Liggins et al. [17] had shown that estrogen increased the $PGF_{2\alpha}$ content of the maternal component of placenta, the endometrium and myometrium, but did not alter $PGF_{2\alpha}$ concentrations in the fetal part of the placenta. Hence, we (Challis, Lye and Gibb 1997 unpublished) suggest that there is little evidence that estrogen can upregulate PGHS-2 expression in fetal tissues and

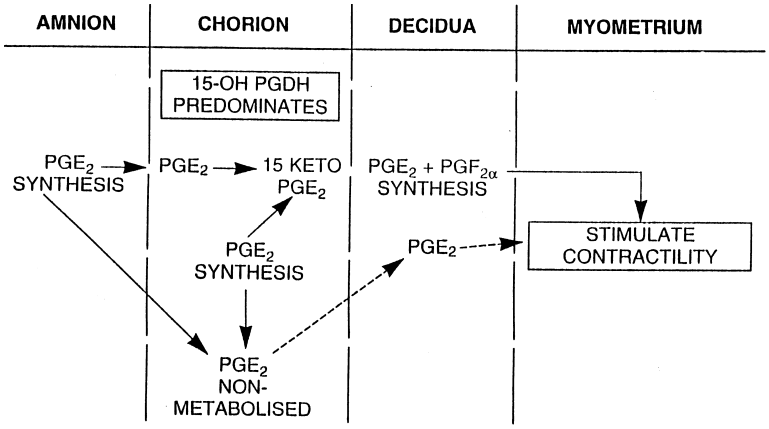

Fig. 3. Compartmentalization of prostaglandin synthesis and metabolism within the human fetal membranes, decidua and myometrium in late gestation

that the sequence of events concerned with regulation of prostaglandin production and parturition in sheep (see above) may need to be re-evaluated.

It is suggested, based in part on the direct stimulatory effects of glucocorticoids on prostaglandin production in human fetal tissues (see below), that in sheep, the rising levels of fetal cortisol directly upregulate PGHS-2 expression in placental trophoblast. This leads to increased PGF_2 synthesis and output from the placenta. This $PGF_{2\alpha}$, acting in a paracrine/autocrine fashion, alters placental $P450_{C17}$ expression, causing an altered pattern of placental steroidogenesis, resulting in a fall in progesterone, and increased estrogen output. Placental estrogen is then responsible for upregulating the contraction-associated proteins (connexin-43, OT-receptor, PG receptors) of the endometrium and myometrium. Estrogen may also be responsible for increased PGHS activity in maternal tissues as one of the final maternal events leading to increased uterotonin production and birth.

Prostaglandins and human parturition

In women, prostaglandin production is discretely compartmentalized within the fetal membranes. In amnion, PGHS activity predominates, $PGF_{2\alpha}$ is the principal prostaglandin formed, and there is an increase in prostaglandin synthase activity and PGHS-2 mRNA in amnion collected from patients at term spontaneous labor compared to term Caesarean section [1]. There are significantly higher levels of PGHS-2 mRNA in amnion from patients in preterm labor [20]. Decidua also has potential for prostaglandin production. Output of PG's from decidual tissue has been reported, in some studies, to be significantly higher at spontaneous labor than from patients at elective Caesarean section [21]. Decidual PG production may result from the activity of PGHS-1, since there is comparatively little PGHS-2 mRNA expressed in this tissue [22].

The chorion, interposed between amnion and decidua, has both PGHS and 15-hydroxyprostaglandin dehydrogenase (PGDH) activities, but the metabolizing enzyme predominates ([23], Fig. 3). Olson and colleagues have shown that the output of prostaglandins, prostaglandin synthase activity, and PGHS-2 mRNA is significantly higher in chorion collected from patients at spontaneous labor compared to patients at elective Caesarean section (D. M. Olson, personal communication). It has been suggested that for much of pregnancy chorion forms a relative metabolic barrier preventing passage of prostaglandins generated within amnion or chorion from reaching underlying decidua or myometrium [24]. This suggests that unless the synthetic activity of amnion/chorion exceeds the metabolic potential of the chorion, prostaglandins driving the myometrium would have to be generated within decidual tissue, or the myometrium itself. Preliminary data suggest that labor is associated with increases in PGHS-2 but not PGHS-1 expression in the human myometrium (Panter and Lye, unpublished).

Prostaglandin synthesis

In human fetal membranes in late gestation, expression of PGHS-2 mRNA occurs in amnion epithelium, in sub-epithelial fibroblasts, and in chorion trophoblasts. PGHS-2 mRNA localizes to blood vessels in decidual tissue, but in general is expressed at low levels in decidual stromal cells of tissue collected from patients at term, in the absence of active labor [22, 25].

The distribution of PGHS-2 mRNA in the human fetal membranes is similar to the pattern of localization of glucocorticoid receptors, detected by immunohistochemistry. Immunoreactive (ir-)Type-2 glucocorticoid receptor (GR) localized to the amnion epithelium, to cells within the sub-epithelial mesenchymal tissue, to the chorion trophoblasts, and to decidual stromal cells [26]. The number of cells that were immunopositive for Type-2 GR was significantly higher in tissues collected fom patients at preterm labor.

It is now clear that *in vitro* glucocorticoids stimulate prostaglandin synthase Type-2 mRNA and activity in human amnion [27–29]. However, the ir-PGHS-2 and PGHS-2 mRNA localizes primarily to the fibroblast cell population of amnion, and not to the amnion epithelial cells [27]. Since both amnion epithelial cells and fibroblasts contain glucocorticoid receptors, the effects of glucocorticoids on PGHS-2 could be direct or indirect. An indirect effect of glucocorticoid on fibroblasts could be mediated through the amnion epithelial cells. These cell types express activators such as corticotrophin-releasing hormone [30]. It is possible that glucocorticoids stimulate output from these cells of locally acting peptides such as CRH, and these then act on the fibroblasts to upregulate prostaglandin production.

Evidence consistent with this proposal has been produced in unpublished studies by Phil Bennett and colleagues in London, England. Bennett has cultured mixed human amnion cell preparations as monolayers, and then treated the cells with corticotrophin-releasing hormone (10^{-8} M). He confirmed observations [31, 32] showing that CRH increased output of prostaglandins (PGE_2) from amnion cells maintained in culture. Using RT-PCR, it was found that CRH teatment increased levels of PGHS-2 mRNA several fold over control cultures, and this correlated with the

increase in PGE_2 output by the cells (P. R. Bennett, personal communication). Thus direct evidence is now available for stimulatory effects of CRH on PGHS-2 expression, and PGE_2 output from amnion cells. These data suggest that glucocorticoids may either stimulate amnion cells directly to produce prostaglandins, or may stimulate adjacent epithelial cells to produce CRH, which in turn stimulate prostaglandin production, and increase PGHS-2 expression from the sub-epithelial fibroblast and macrophage layer.

In vitro studies have delineated many other factors that increase prostaglandin output by human fetal membranes [1, 37]. Importantly, cytokines, produced in the setting of infection can upregulate expression of PLA_2 and PGHS-2, and increase PG output. Growth factors, including EGF and TGF also promote PG biosynthesis. At pesent, however, extrapolation from these *in vitro* measurements to the physiologic regulation of enhanced PG output *in vivo* remains speculative, and is limited to generating a (growing) list of potential agonists.

Prostaglandin metabolism

Chorion trophoblasts express abundant 15-hydroxyprostaglandin dehydrogenase (PGDH). Cheung et al. [24] using immunohistochemistry, found that approximately 60–70% of chorion trophoblast cells were immunopositive for PGDH in most preparations of membranes from patients at term. PGDH was not detected in amnion, nor in the underlying decidual tissue. Studies by Sangha et al. [33] showed that a subset of patients in idiopathic preterm labor in the absence of infection had very low levels or absent PGDH in chorionic trophoblast cells. In these patients, there was a corresponding reduction in PGDH activity, and in PGDH mRNA, determined by northern blotting. Approximately 10–15% of patients presenting in idiopathic preterm labor did so in association with a relative deficiency of the PGDH enzyme. The activity and levels of ir-PGDH in membranes from patient in preterm labor with an underlying infective process are also extremely low [34]. Loss of PGDH in the presence of infection is associated with the destruction and loss of the chorionic trophoblast cells.

The mean level of PGDH activity ($PGF_{2\alpha}$ to PGFM conversion) in chorion was lower in patients at spontaneous labor compared to that at Caesarean section at term [35]. It was reduced further in patients in idiopathic preterm labor and further still in patients in preterm labor in the presence of an underlying infective process. The loss of PGDH expression was specific for chorion, because there were no changes in PGDH activity in placental tissue from these same groups of patients. Levels of PGDH mRNA followed essentially the same pattern.

We suggest that in normal pregnancy, PGDH expression and activity in chorion is high (Fig. 4). Prostaglandins generated within amnion or chorion are rapidly metabolized and pass to decidua and myometrium in only very small amounts, Thus the prostaglandins that drive myometrial activity seem likely to be derived from decidua or myometrium. It is not surprising that until recently it had been very difficult to demonstrate changes in prostaglandin concentrations in amniotic fluid in association with labor in normal patients [36], since it seems unlikely that prostaglandin concentrations in amniotic fluid reflect at all in absolute terms, levels produced

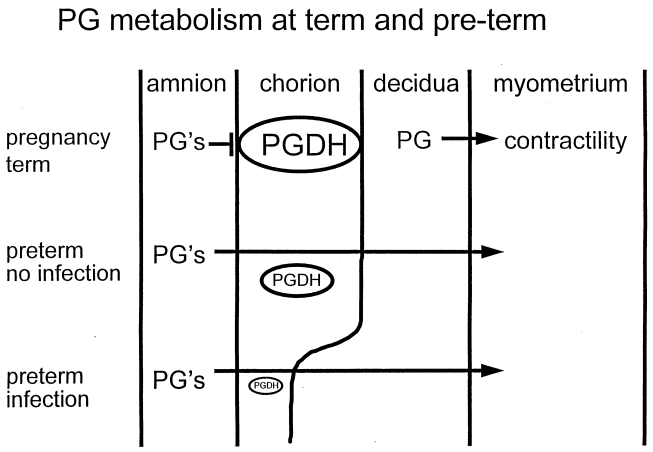

Fig. 4. Prostaglandin metabolism at term, and at preterm labour in the absence, or in the presence of infection

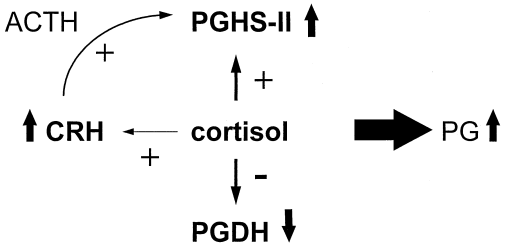

Fig. 5. Postulated relationships between cortisol and prostaglandin synthase in intrauterine tissues. CRH, corticotrophin-releasing hormone; PGHS-2, prostaglandin synthase type 2; PGDH, 15-hydroxyprostaglandin dehydrogenase

locally in decidua and/or myometrium. In some patients in idiopathic preterm labor levels of chorionic PGDH are clearly reduced. In these patients prostaglandin generated within amnion or chorion, in response to a variety of potential stimuli, would be metabolized only poorly, and could therefore pass to the underlying decidual tissue and myometrium. In patients with infection, where trophoblasts are destroyed, PGDH activity is lost. In these patients potent prostaglandin synthetic machinery is established [37], and in the absence of metabolism, those prostaglandins are likely to provide a potent drive to myometrial concentrations.

Figure 5 indicates our current thinking on the interrelationships between prostaglandins and glucocorticoids in human intrauterine tissues in late pregnancy, and at labor. Elevated levels of glucocorticoids stimulate prostaglandin production by increasing expression of PGHS-2 mRNA in trophoblast cells, and thereby increasing the output of prostaglandin E_2. Glucocorticoids also decrease activity of the

prostaglandin-metabolizing enzyme, PGDH (Patel, Clifton and Challis, unpublished), and stimulate output of CRH. CRH promotes prostaglandin synthase expression and PG output at least by amnion cells. Collectively therefore, these pathways contribute to increased prostaglandin production by intrauterine tissues. Increased production of the uterotonins, acting through appropriate stimulatory receptor subtypes participate in the drive to contractile activity and parturition. Finally, it should be remembered that not all PG receptors are stimulatory. Effects of PGE_2 on EP_2 and EP_4 receptors may be very important in relaxing smooth muscle, particularly in the lower uterine segment. In unpublished studies, Teoh and Lye have found significant increases in expression of EP_4 receptor in myometrium of the lower uterine segment with the onset of labor. This might allow passage of the fetus through the lower segment while prostaglandins acting through EP_1 and EP_3 receptors in other areas of the uterus, promote contractility.

Acknowledgements

Work in the author's laboratory was supported through the Canadian Medical Research Council (MRC Group in Fetal and Neonatal Health and Development). The author would like to acknowledge particularly the help and assistance of Drs. William Gibb and Steven Lye in the conduct of these experiments, and Mrs. Linda Vranic for her help in the preparation of the manuscript.

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Warum ist die antepartale Sterblichkeit höher als die frühe Neonatalsterblichkeit?

H.-K. Selbmann

Fakten

Die Beantwortung der Frage „Warum ist die antepartale Sterblichkeit höher als die frühe Neonatalsterblichkeit?“ scheint auf den ersten Blick einfach zu sein. Beim zweiten Blick machen sich allerdings schnell die ersten Schwierigkeiten bemerkbar. Sie fangen bei den Definitionen und der Datenlage an und hören bei der Suche nach möglichen Gründen für eventuelle Unterschiede auf. Erwarten Sie jedoch von einem Epidemiologen keine endgültigen Antworten auf eine Frage, an deren Beantwortung sich nach Durchsicht der Literatur wohl noch kaum jemand bisher gewagt hat.

Zunächst bestätigt ein Blick auf die verfügbaren Daten des Statistischen Bundesamtes die Aussage (Tabelle 1): In der Bundesrepublik Deutschland war die antepartale Sterblichkeit in den Jahren 1992 bis 1994 stets höher als die Frühneonatalsterblichkeit gewesen und wird dies auch in Zukunft sein. Während sie in den Jahren 1992 und 1993 in etwa in der Mitte zwischen Neonatal- und Frühneonatalsterblichkeit lag, machte sie in 1994 einen kräftigen Sprung nach oben (auf 3,6 ‰)

Tabelle 1. Fakten in Promille (Statistisches Bundesamt)

Sterblichkeit	1992	1993	1994
Antepartale Sterblichkeit[a]	3,0	2,8	3,6
Frühneonatalsterblichkeit (1.–7. Tag)	2,5	2,4	2,4
Neonatalsterblichkeit (1.–28. Tag)	3,4	3,2	3,3
Säuglingssterblichkeit (bis 1 Jahr)	6,1	5,8	6,0

[a] Geschätzt als 90% der amtlichen Totgeburtlichkeit, da die Daten des Statistischen Bundesamtes keine Unterscheidung zwischen ante- und subpartaler Totgeburtlichkeit kennen.

und lag sogar über der Neonatalsterblichkeit. Der Grund für diesen Sprung liegt jedoch nicht in einem veränderten Leistungsgeschehen, sondern in einer Änderung der amtlichen Definition „Totgeburtlichkeit“.

Definitionen

Die Definitionen der antepartalen Sterblichkeit und der frühen Neonatalsterblichkeit enthalten zum Teil natürliche, zum Teil statistische Unschärfen, die sie interpretationsfähig machen.

Eine *Totgeburt* ist definiert als ein ohne Lebenszeichen (mindestens eines der Kriterien: Herzschlag, Einsetzen der natürlichen Atmung oder Pulsieren der Nabelschnur muß erfüllt sein) geborenes Kind mit einem Geburtsgewicht von mindestens 500 g. Bis zu der erfreulichen Änderung des Personenstandsgesetzes zum 1. 4. 1994 lag die Mindestgewichtsgrenze bei 1 000 g. Bereits mehrere Jahre zuvor hatten die meisten Perinatologischen Arbeitsgemeinschaften diese Änderung durch ihre Empfehlung an die Kliniken, alle Geborenen ab 500 g in die Perinatalerhebungen aufzunehmen, schon vorweggenommen.

Die amtliche Senkung des Mindestgeburtsgewichts bei Totgeborenen hat zur Folge, daß ab 1994 in Deutschland die Zeitreihen der Totgeburtlichkeit und der Perinatalen Mortalität – nicht jedoch der Neonatalsterblichkeiten – neu bewertet werden müssen. Geändert haben sich durch die Änderung der Mindestgewichtsgrenze bei Totgeburten auch die Relationen der geburtshilflichen Qualitätsindikatoren zu einander (s. Tabelle 1).

Eine *antepartale Totgeburt* eine Totgeburt, die vor Geburtsbeginn (mindestens eines der Kriterien: Regelmäßige Wehen alle 10 min, Sprung der Fruchtblase oder Ausstoßung des Zervixschleimpropfes muß erfüllt sein) geboren wurde. Die Abgrenzung zur subpartalen Totgeburt ist insbesondere bezüglich der Regelmäßigkeit der Wehen interpretationsfähig. Zudem unterscheidet die amtliche Statistik nicht zwischen ante- und subpartaler Sterblichkeit.

Eine Abschätzung des Anteils der subpartal verstorbenen Kinder an allen Totgeborenen kann nur an Hand der Daten der Perinatalerhebungen vorgenommen werden. Abbildung 1 zeigt den zeitlichen Verlauf des Anteils der subpartal verstorbenen Kinder an den Totgeborenen in der Bayerischen Perinatalerhebung. Bei den Totgeborenen ab 1 000 g liegt er einigermaßen konstant bei ca. 9–10 %. Der Einbruch im Jahr 1990 (ca. 30 Kinder) ist nicht erklärbar. Der Anstieg des Anteils subpartal

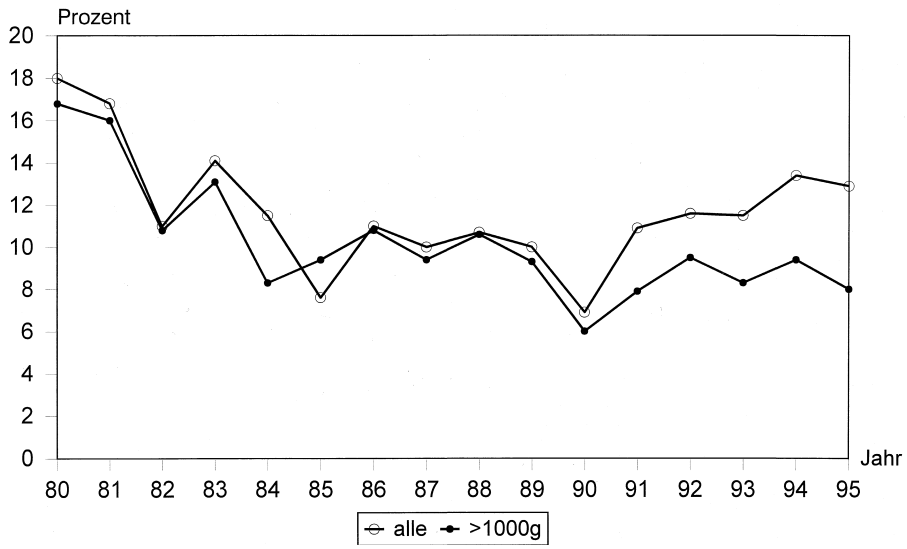

Abb. 1. Zeitlicher Verlauf des Anteils der subpartal verstorbenen Kinder an den Totgeborenen in der Bayerischen Perinatalerhebung

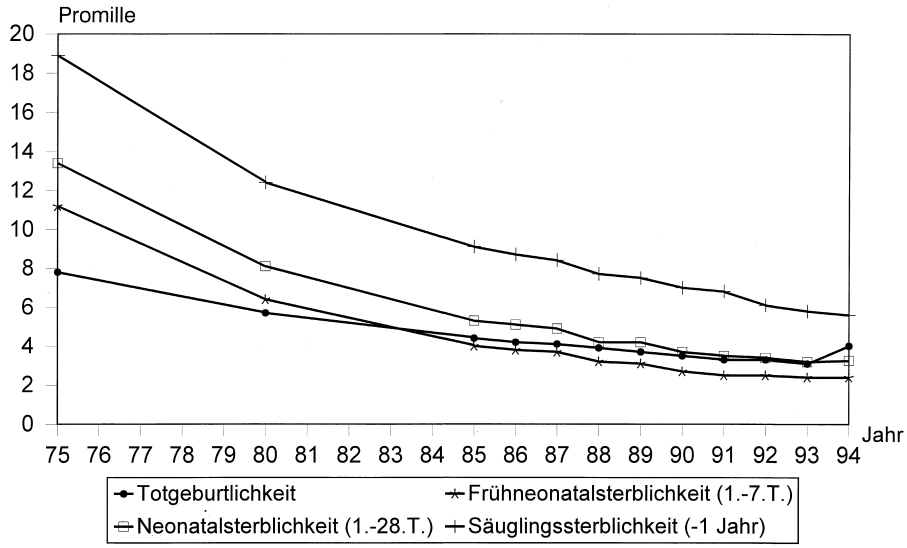

Abb. 2. Entwicklung der Totgeburtlichkeit, Frühneonatal-, Neonatal- und Säuglingssterblichkeit in Deutschland (alte und neue Bundesländer zusammen) im Verlauf von 20 Jahren (Quelle: Jahrbücher des Statistischen Bundesamtes)

verstorbener Kinder an allen Totgeborenen ab 1991 ist auf die bereits erwähnte Vorwegnahme der Personenstandsgesetzänderung in den Perinatalerhebungen zurückzuführen.

Frühneonatalsterblichkeit und Neonatalsterblichkeit sind definiert als die Anteile der zwischen dem 1. und 7. bzw. 1. und 28. Tag Verstorbenen an allen lebendgeborenen Kindern. Nur wenige Geburtskliniken kennen wegen der fehlenden systematischen Rückmeldung ihre Neonatalsterblichkeit und selbst die Frühneonatalsterblichkeit ist nicht immer exakt bekannt. Auch die amtliche Statistik hat damit ihre Schwierigkeiten, da zur exakten Berechnung der Neonatalsterblichkeiten eine – nicht immer und in allen Bundesländern durchgeführte – Zusammenführung der Geburts- und der Todesbescheinigungen notwendig ist.

Die Grenze zwischen der Früh- und der Spätneonatalsterblichkeit (8.–28. Tag) erscheint heute etwas arbiträr zu sein, denn mit dem derzeitigen Stand der Neonatalmedizin ist die Erreichung des 7. Lebenstages selbst für einen Anenzephalus kein Problem mehr. Die Gefahr, daß Neugeborene nur aus dem Kompartment der Frühneonatalsterblichkeit in das Kompartment der Spätneonatalsterblichkeit wechseln, ist nicht von der Hand zu weisen.

Frühneonatalsterblichkeit und *Neonatalsterblichkeit* haben per definitionem einen anderen Populationsbezug als die Totgeburtlichkeit. Für die folgenden statistischen Vergleiche zwischen der antepartalen und der frühneonatalen Sterblichkeit wird letztere daher als der Anteil der zwischen dem 1. und 7. Tag Verstorbenen an allen Tot- und Lebendgeborenen neu definiert. So definiert addieren sich zudem Totgeburtlichkeit und Frühneonatalsterblichkeit zur perinatalen Mortalität und ein im Verlauf der Zeit gleichbleibendes Verhältnis von Totgeburtlichkeit zu perinataler Mortalität besagt, daß sich Totgeburtlichkeit und neu definierte Frühneonatalsterblichkeit gleichförmig verändern.

Die eingangs gestellte Frage läßt sich – wenig befriedigend – allein durch die oft interpretationsfähigen und zum Teil arbiträren Definitionen erklären. Interessanter ist jedoch die im folgenden zu diskutierende Frage: *"Warum verbesserte sich in den vergangenen 20 Jahren die antepartale Sterblichkeit nicht in gleichem Maße wie die (neu definierte) frühe Neonatalsterblichkeit?*

Daß dem so ist, zeigt Abb. 2. Zwischen 1975 und 1993 sanken in der Bundesrepublik Deutschland (alte und neue Bundesländer zusammen) die Säuglingssterblichkeit um 69 %, die Neonatalsterblichkeit um 76 % und die Frühneonatalsterblichkeit um 79 %, aber die Totgeburtlichkeit nur um 60 %. Bedauerlicherweise enthalten die Jahrbücher des Statistischen Bundesamtes wegen der begrenzten Verfügbarkeit der Neonatal- und Säuglingsterblichkeiten der ehemaligen DDR die Qualitätsindikatoren nur in 5 Jahresabständen für die ersten 10 Jahre des Beobachtungszeitraumes.

Nationale, internationale, und regionale Vergleiche im Verlauf der Zeit

Neben der beeindruckenden Senkung aller Qualitätsindikatoren der Geburts- und Neonatalperiode zeigt Abb. 2 noch 3 weitere Effekte:

– den Anstieg der Totgeburtlichkeit in 1994 auf Grund des geänderten Personenstandsgesetzes,

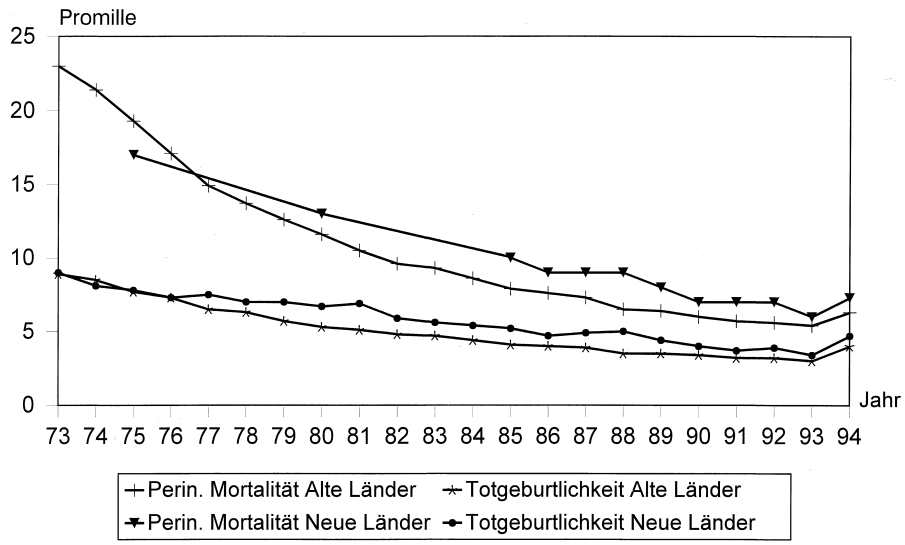

Abb. 3. Entwicklung von Totgeburtlichkeit und Perinataler Mortalität in den alten und den neuen Bundesländern Deutschlands (Quelle: Jahrbücher des Statistischen Bundesamtes)

– die gleichförmige Senkung von Neonatal- und Frühneonatalsterblichkeit, die nicht auf eine Verschiebung der Frühneonataltodesfälle in die Spätneonatalperiode hindeutet, und
– die Überschneidung von Totgeburtlichkeit und Frühneonatalsterblichkeit zwischen 1983 und 1984.

Betrachtet man Totgeburtlichkeit und perinatale Mortalität getrennt für die *alten und neuen Bundesländer Deutschlands*, so stellt man fest, daß die alten Bundesländer in den Jahren ab 1977 stets besser als die neuen abgeschnitten haben, ohne daß sich die Unterschiede jedoch im Verlauf der Jahre erheblich vergrößert hätten (Abb. 3).

Wenn der Anteil der Totgeburten an den perinatal verstorbenen Kindern kontinuierlich ansteigt, ist dies ein Zeichen dafür, daß die Totgeburtlichkeit nicht in gleichem Maße sinkt wie die (neu definierte) Frühneonatalsterblichkeit. Genau dies ist aber sowohl für die alten als auch die neuen Bundesländer seit 1975 der Fall (Abb. 4). Der Hauptanstieg – etwas steiler in den alten Bundesländern – fand zwischen 1975 und 1985 statt. Ein Grund dafür könnte sein, daß die Neonatalmedizin in dieser Zeit erheblich erfolgreicher im Verhindern von Todesfällen war als die Geburtshilfe. Aber auch zwischen 1985 und 1993 verlor die Totgeburtlichkeit in beiden Landesteilen weiter an Boden. Erstaunlich ist dabei die Gleichförmigkeit, denn immerhin nahm in dieser Zeit die Geburtenzahl in den neuen Bundesländern um 60 % ab, während sie in den alten Bundesländern zwischenzeitlich um 6 % zugenommen hatte. Das Jahr 1994 ist wieder geprägt durch die Änderung des Personenstandsgesetzes. Nunmehr sind nahezu 2 Drittel aller perinatal verstorbenen Kinder Totgeburten.

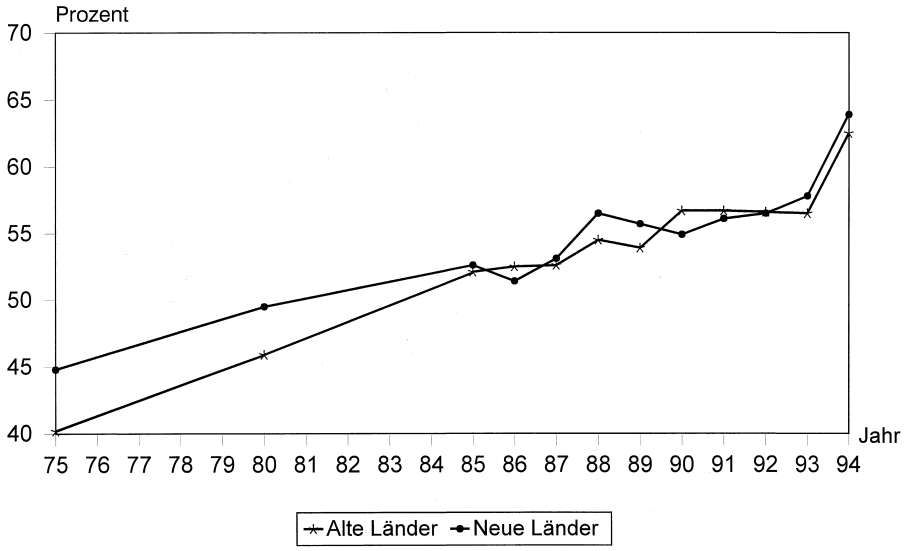

Abb. 4. Anteil der Totgeburten an den perinatal Verstorbenen in den alten und den neuen Bundesländern (Quelle: Jahrbücher des Statistischen Bundesamtes)

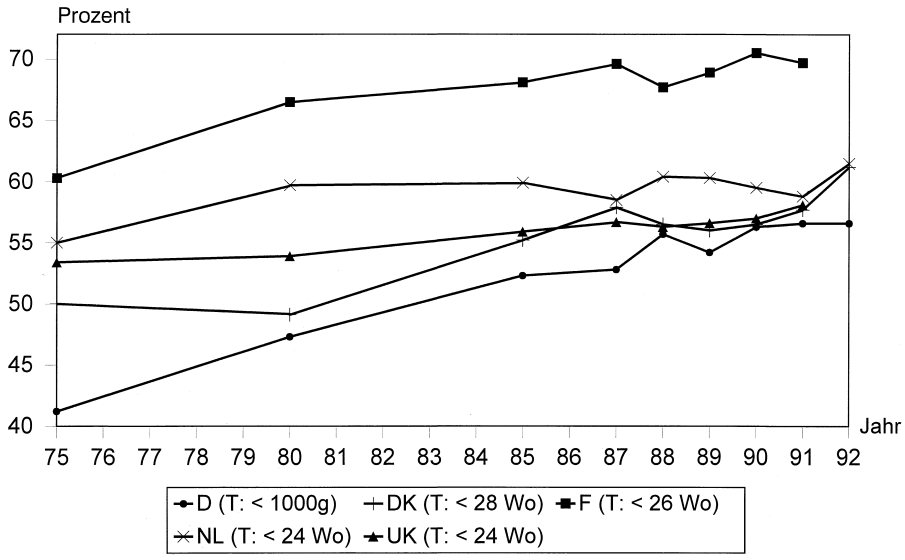

Abb. 5. Anteil der Totgeburten an den perinatal Verstorbenen im internationalen Vergleich (Quelle: Eurostat)

Internationale Vergleiche der perinatalen Mortalität hinken wegen der unterschiedlichen Definition der Totgeburten immer. So schließen zum Beispiel Großbritannien und die Niederlande alle Totgeborenen unter 24, Frankreich unter 26 und Dänemark alle unter 28 Schwangerschaftswochen bei der Berechnung der Totge-

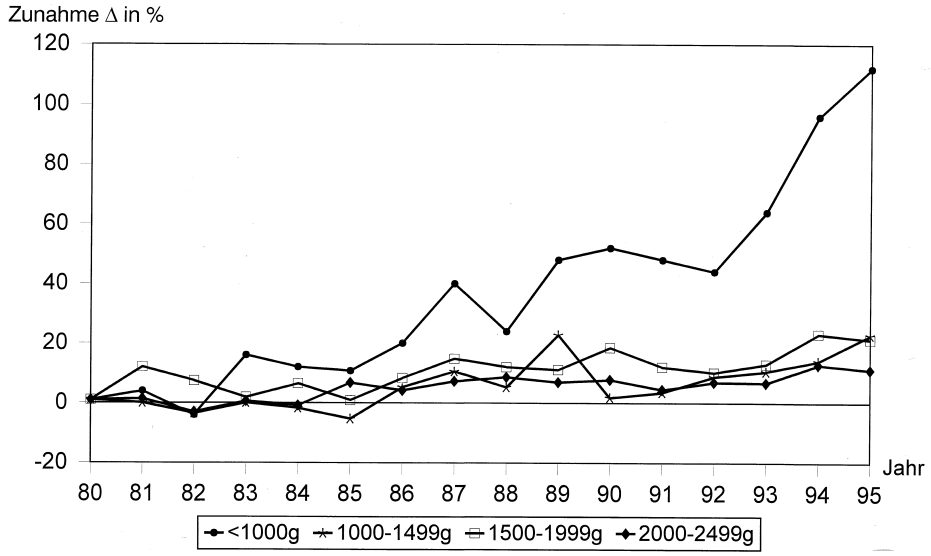

Abb. 6. Zunahme der Geburten in den unteren Geburtsgewichtsklassen gegenüber 1980 in der Bayerischen Perinatalerhebung

burtlichkeit aus. Der deutschen Mindestgeburtsgewichtsgrenze von 1 000 g (bis 31.3.1994) am nächsten kommt wohl die dänische Definition mit 28 SSW. Im internationalen Vergleich besonders auffällig verhält sich der Anteil der Totgeburten an den perinatal Verstorbenen in Frankreich (Abb. 5). Dies liegt an der französischen Totgeburtenrate, die in Europa zu den höheren gehört, während Frankreich bezüglich der Frühneonatalsterblichkeit in Europa an der Spitze steht.

Besonders auffällig ist auch Großbritannien mit einem sehr niedrigen Totgeburtenanteil, obwohl dort nur die Totgeburten bis zur 24. SSW aus der Berechnung der Totgeburtlichkeit ausgeschlossen werden; ein Zeichen dafür, daß die Frühneonatalsterblichkeit verhältnismäßig hoch sein muß. Nicht erstaunlich ist, daß sich das Verhältnis Totgeburtlichkeit zu perinataler Mortalität in den Niederlanden und Großbritannien zwischen 1975 und 1991 kaum verändert hat, weil dort schon immer nur Totgeburten unter 24 SSW aus der Berechnung der Totgeburtlichkeit ausgeschlossen worden sind. Deutschland ist nur auf Grund seiner niedrigen Totgeburtenrate europäischer Spitzenreiter in der perinatalen Mortalität. Dies hat sich ab 1994 geändert.

Einfluß des Geburtsgewichts

Ein wesentlicher Grund für die geringere Abnahme der Totgeburtlichkeit gegenüber der Frühneonatalsterblichkeit könnte in der zahlenmäßigen Zunahme der unteren Geburtsgewichtsklassen mit den höheren Mortalitätsraten liegen. In der Tat haben nach den Statistiken der Bayerischen Perinatalerhebung zwischen 1980 und 1995 die unteren Geburtsgewichtsklassen erheblich zugenommen: die Kinder zwi-

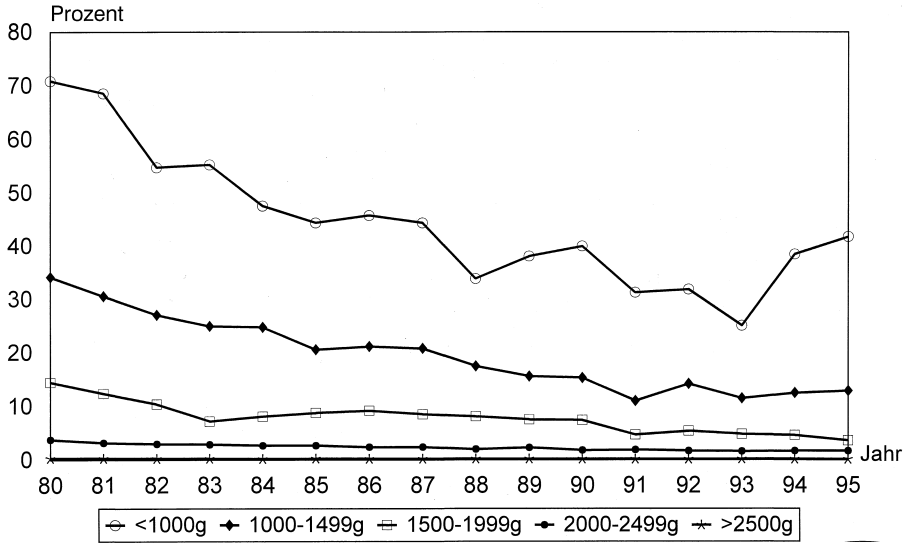

Abb. 7. Abnahme der Perinatalen Mortalität nach Geburtsgewichtsklassen in der Bayerischen Perinatalerhebung

schen 2 499 und 2 000 g um 11 %, zwischen 1 999 und 1 500 g um 21 %, zwischen 1 499 und 1 000 g um 23 % und unter 1 000 g sogar um 112 % (Abb. 6). Bei letzteren macht sich seit 1994 wiederum die Änderung des Personenstandsgesetzes deutlich bemerkbar. Es scheint so, als ob die Vorwegnahmeeffekte der Änderung der Personenstandsgesetzes in den Perinatalerhebungen seit 1990 auch zu einem deutlicheren Anstieg der Geburten zwischen 1 000 und 1 499 g geführt haben. Der Sprung der Geburtenzahlen in dieser Gewichtsklasse in 1989 kann nicht erklärt werden.

Die zu den Geburtsgewichtsklassen gehörende perinatale Mortalität ist Abb. 7 zu entnehmen. Zwischen 1980 und 1993 nahm die perinatale Mortalität der Kinder zwischen 2 499 und 2 000 g um 58 %, zwischen 1 999 und 1 500 g um 67 %, zwischen 1 499 und 1 000 g um 66 % und unter 1 000 g um 65 % ab. Die Abnahme der perinatalen Mortalität zwischen 58 und 66 % oder fast 5 % pro Jahr ist sicher ein Verdienst der gesteigerten Qualität von Geburtshilfe und Neonatalversorgung. Mit Ausnahme der Geburtsgewichtsklasse unter 1 000 g setzte sich dieser Abwärtstrend auch in den Jahren 1994 und 1995 fort. Bei den Kindern unter 1 000 g machte sich jedoch die Änderung des Personenstandsgesetzes wieder bemerkbar: die Zahl der Totgeborenen unter 1 000 g verdrei- bis -vierfachte sich zwischen 1993 und 1995.

Doch zurück zu der Frage, ob der in Abb. 4 dargestellte unterschiedliche Rückgang von antepartaler Sterblichkeit gegenüber der (neu definierten) Frühneonatalsterblichkeit für alle Geburtsgewichtsklassen gleichermaßen zutrifft. Dazu wurde an Hand der Daten der Bayerischen Perinatalerhebung getrennt für alle Geburtsgewichtsklassen der Anteil der Totgeborenen an den perinatal verstorbenen Kindern berechnet und in Abb. 8 mit Hilfe gleitender Mittelwerte graphisch dargestellt.

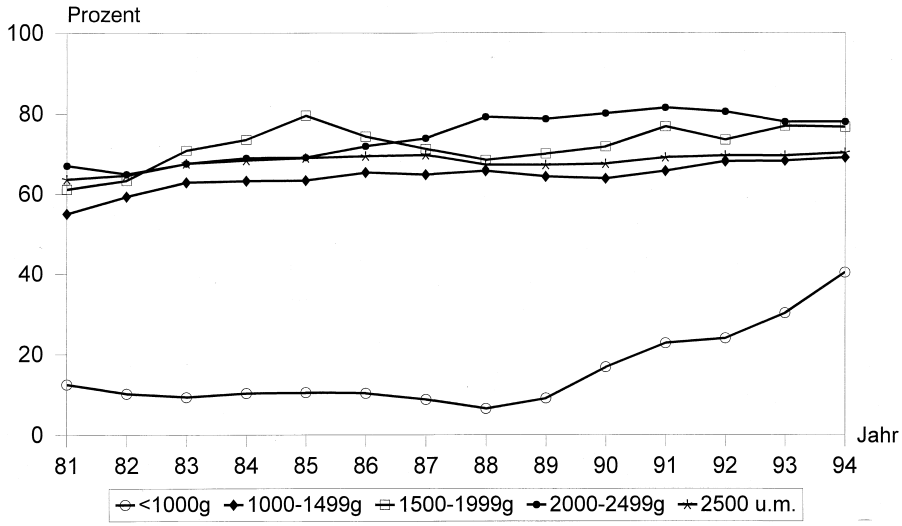

Abb. 8. Veränderungen des Anteils der Totgeborenen an den perinatal verstorbenen Kindern in der Bayerischen Perinatalerhebung (gleitende Mittelwerte aus drei Jahreswerten)

Der Abb. 8 lassen sich für die einzelnen Geburtsgewichtsklassen im Zeitraum von 1980 bis 1995 folgende Beobachtungen entnehmen:

- Die Zahl der Totgeborenen ist in allen Gewichtsklassen stets größer als die Zahl der frühen Neonatal-Verstorbenen (Anteil der Totgeburten an der perinatalen Mortalität immer größer als 50 %), ausgenommen die Geburtsgewichtsklasse bis 1 000 g.
- Bei den Kinder über 2 500 g verbesserten sich Totgeburtlichkeit und Frühneonatalsterblichkeit gleichmäßig zwischen 1981 und 1994 (Anteil Totgeburten ca. 69 %). Offensichtlich waren Geburtshelfer und Neonatologen bei den reif geborenen Kindern gleichermaßen erfolgreich bzw. gelang es beiden nicht, spektakuläre Erfolge zu verwirklichen.
- Bei den Kindern zwischen 2 499 und 2 000 g verbesserten sich Totgeburtlichkeit und Frühneonatalsterblichkeit gleichmäßig zwischen 1988 und 1994 (Anteil Totgeburten ca. 80 %). Davor hatte jedoch die Zahl der frühen Neonatal-Verstorbenen schneller abgenommen als die der Totgeburten.
- Bei den Kindern zwischen 1 999 und 1 500 g nahm seit 1988 die Frühneonatalsterblichkeit schneller ab als die Totgeburtlichkeit. 1994 landete das Verhältnis von Totgeburtlichkeit zu perinataler Mortalität auf dem gleichen Niveau wie das der nächst höheren Gewichtsklasse (Anteil Totgeburten ca. 80 %). Dafür, daß es dort 1985 schon einmal war, fehlt eine Erklärung.
- Bei den Kindern zwischen 1 499 und 1 000 g verbesserten sich Totgeburtlichkeit und Frühneonatalsterblichkeit gleichmäßig zwischen 1983 und 1994. Der Anteil von ca. 66 % Totgeburten an der perinatalen Mortalität läßt, verglichen mit den nächst höheren Geburtsgewichtsklassen, eine weitere Steigerung erwarten.

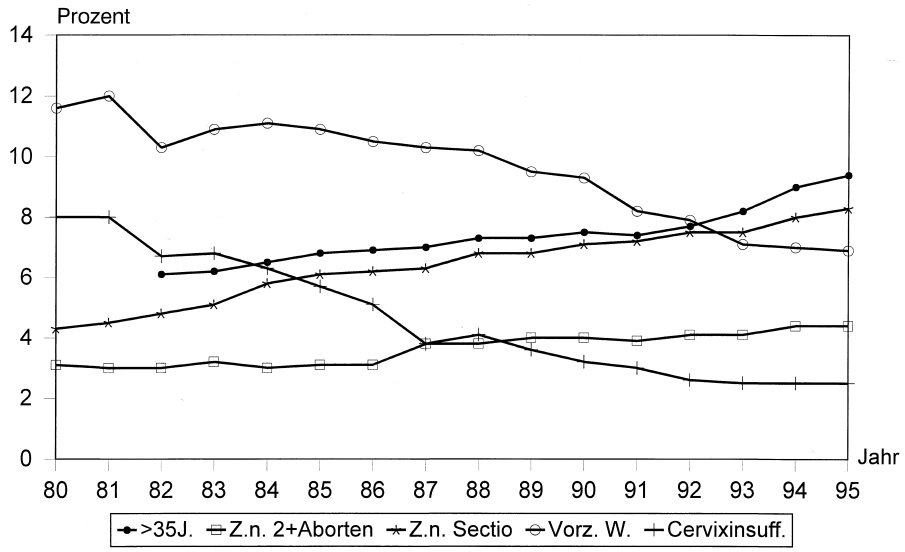

Abb. 9. Veränderungen von einigen Schwangerschaftsrisiken in der Bayerischen Perinatalerhebung

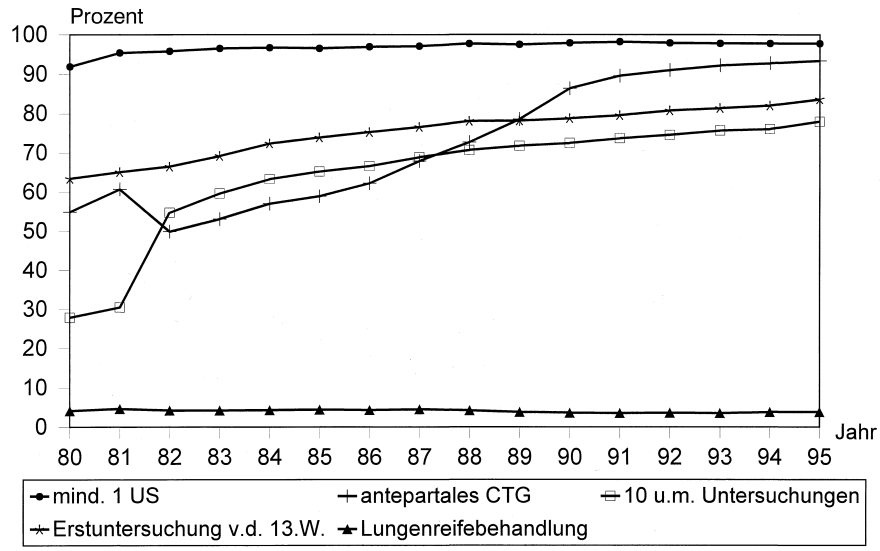

Abb. 10. Veränderungen der Schwangerschaftsbetreuung in der Bayerischen Perinatalerhebung

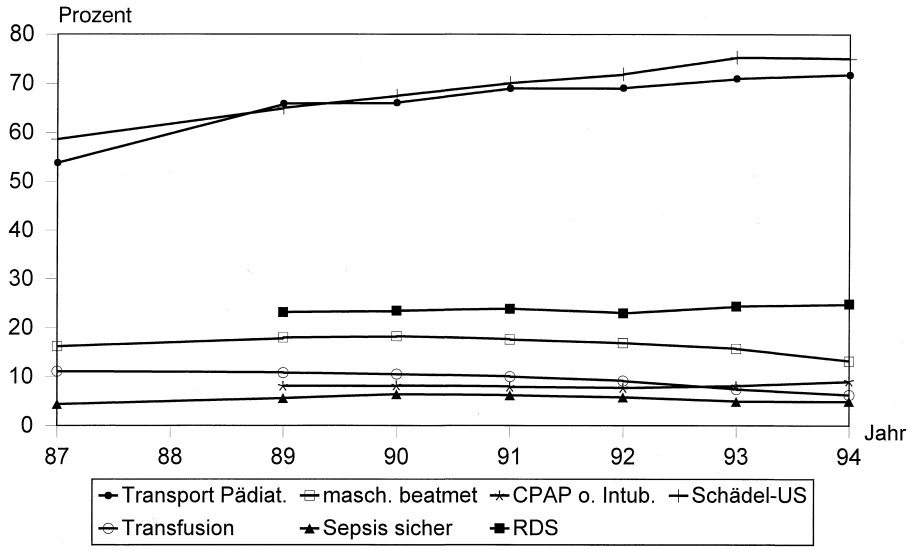

Abb. 11. Veränderungen von einigen Neonatalrisiken und der Neonatalversorgung in der Bayerischen Neonatalerhebung

– Bei den Kindern unter 1 000 g dominierte hauptsächlich der Vorwegnahmeeffekt der Personenstandsgesetzänderung ab 1990.

Zusammenfassend läßt sich also festhalten, daß die Reduktion von Totgeburtlichkeit und Frühneonatalsterblichkeit in den verschiedenen Geburtsgewichtsklassen unterschiedlich verlief. Die Gewichtsklassen zwischen 1 500 und 2 499 g haben in den letzten Jahren erheblich aufgeholt.

Veränderungen von Schwangerschaftsrisiken, Schwangerschaftsüberwachung, Geburtsmanagement und Neonatalversorgung

Die Perinatal- und Neonatalerhebungen können mit ihren Daten Hinweise auf einige nicht unerhebliche Veränderungen der *Schwangerschaftsrisiken*, der Schwangerschaftsüberwachung, des Geburtsmanagements und der Neonatalversorgung im Verlauf der Jahre geben. So haben zwischen 1982 und 1995 Erstgebärende über 35 Jahre um gut ein Drittel zugenommen, während die Geburtenziffer von 1,45 auf 1,22 abfiel (Abb. 9).

Ebenfalls zugenommen hat der Zustand nach Kaiserschnitt (von 4,3 auf 8,3 %) und der Zustand nach 2 und mehr Aborten (von 3,1 auf 4,4 %). Bei den beobachteten steigenden Zahlen untergewichtiger Neugeborenen (s. Abb. 6) überraschend stark rückläufig waren vorzeitige Wehen (von 11,6 auf 6,9 %) und die Zervixinsuffizienz (von 8,0 auf 2,5 %).

Die Schwangerschaftsüberwachung hat durch 11 Novellen der Mutterschaftsrichtlinien an Frühzeitigkeit und Intensität zugenommen (Abb. 10). Unter anderem

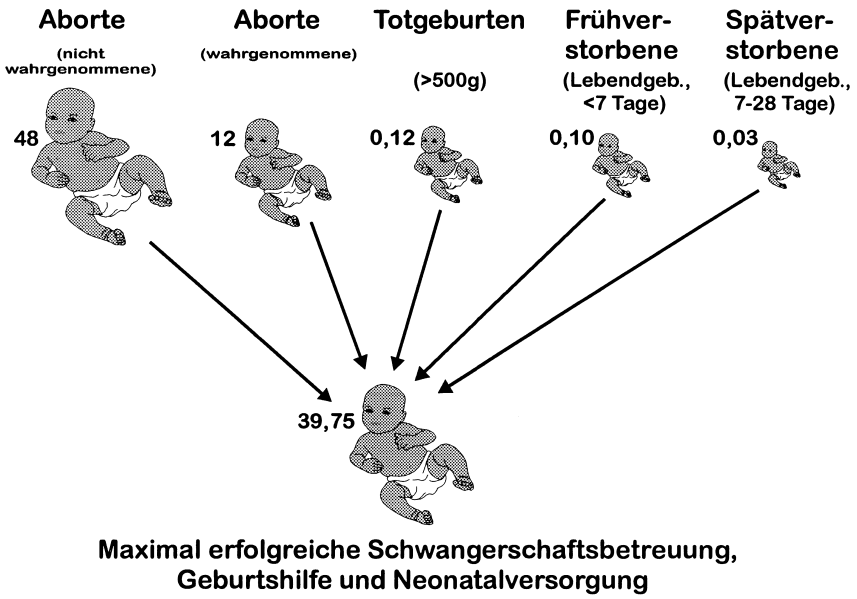

Abb. 12. Kompartments der Peri- und Neonatalversorgung

wurden in Deutschland als erstem europäischem Land schon 1980 Ultraschalluntersuchungen mit der Möglichkeit der Erkennung von Fehlbildungen und Wachstumsretardierungen in die Mutterschaftsvorsorge aufgenommen.

Obwohl die Frühzeitigkeit des Überwachungsbeginns (vor der 13. SSW) und die Häufigkeit der Teilnahme (10 und mehr Untersuchungen) in den 15 Jahren stetig zugenommen haben, bleibt auch in 1995 von 16 % bzw. 22 % der Schwangeren zu berichten, die erst nach der 13. SSW zur ersten Schwangerschaftsuntersuchung kamen bzw. bei der Geburt weniger als 10 Untersuchungen aufwiesen. Lungenreifebehandlungen blieben weitgehend konstant. Die Datenbrüche beim antepartalen CTG und der Häufigkeit der Teilnahme an der Schwangerschaftsüberwachung in 1981 sind auf Veränderungen des Auswertungsprogramms zurückzuführen.

Im *Geburtsmanagement* waren die größten Veränderungen zwischen 1980 und 1995 bei der pH-Bestimmung (von 15 auf 93 %), der Kaiserschnittfrequenz (von 11,3 auf 17,7 %), der Wehenmittelgabe (von 57 auf 34 %) und der Pufferung (von 3,5 auf 0,2 %) zu beobachten. Regelwidrige Schädellagen, Beckenendlagen und Querlagen waren über die Jahre konstant geblieben.

Leider liegen zur *Neonatalversorgung* flächendeckende Daten erst seit 1987 vor (Abb. 11).

Lediglich die Surfactant-Therapie wurde in diesem Zeitraum breit etabliert, CPAP (seit 1978) und Pulsoximetrie (seit 1986) standen schon länger zur Verfügung. Die größten Veränderungen fanden sich in der Neonatalversorgung beim Schädelsonogramm (von 59 auf 75 %) und beim vom Pädiater begleiteten Transport der Neugeborenen (von 54 auf 72 %). Bei der maschinellen Beatmung (von 16 auf 13 %) und bei Transfusion (von 11 auf 6 %) setzte sich eine strengere Indikationsstellung

durch. CPAP/Intubation, Sepsen, RDS oder Bilirubin über 10 mg/dl blieben weitgehend konstant.

Zusammenfassend läßt sich festhalten, daß sich Schwangerschaftsrisiken und -überwachung, Geburtsmanagement und Neonatalversorgung in den 15 Beobachtungsjahren erheblich verändert haben, ohne daß man jedoch Ursachen für die geringere Reduktion der Totgeburtlichkeit im Vergleich zur Frühneonatalsterblichkeit ausmachen kann.

Je größer der medizinische Fortschritt, desto kranker wird die Bevölkerung.

Der allgemeine medizinische Fortschritt könnte dazu führen, daß die Zahl der Totgeburten, der Neonatal-Verstorbenen, der verstorbenen Säuglinge und der Behinderten in der Bevölkerung immer größer wird. In Abb. 12 sind 6 chronologisch geordnete Kompartments „Nicht wahrgenommener Abort", „Wahrgenommener Abort", „Totgeburt", „Frühneonatal verstorbenes Kind", „Spätneonatal verstorbenes Kind" und „Den 28. Tag überlebendes Kind" symbolisch dargestellt. In einem komplizierteren Modell wäre auch noch die Morbidität als Charakteristikum von Kompartments zu berücksichtigen.

Angenommen 60 % der Konzeptionen werden mit einem Abort abgeschlossen – 20 % davon von der Mutter wahrgenommen – dann führen unter Zugrundelegung der gegenwärtigen Verhältnisse 39,75 % der Konzeptionen zu einem den 28. Tag überlebenden Kind. Die restlichen 0,25 % verteilen sich auf die 3 Kompartments „Totgeburt", „Früh-" und „Spätneonal verstorbenes Kind", deren Verkleinerung bekanntlich das primäre Ziel der Geburtshilfe und Neonatalversorgung ist. Ideale soziale Bedingungen und maximale Schwangerschaftsüberwachung, Geburtsmanagement und Neonatalversorgung würden dazu führen, daß alle Konzeptionen im Kompartment „Den 28. Tag überlebendes Kind" enden. Es könnte aber auch sein, daß der – nicht maximale – medizinische Fortschritt nur zu einem Wechsel des Neugeborenen in das chronologisch folgende Kompartment führt: aus Aborten würden dann Totgeborene, aus Totgeborenen frühneonatal verstorbene Kinder und aus frühneonatal verstorbenen Kindern spätneonatal verstorbene. Das Kompartment der Totgeborenen verfügt dann über das mit Abstand größte Reservoir. Auch dies könnte also ein Grund für die geringere Reduktion der Totgeburtlichkeit gegenüber der Frühsterblichkeit in den letzten 15 Jahren sein.

Zusammenfassung und Schlußfolgerungen

- Große Verbesserungen wurden in der Geburtshilfe und der Neonatalmedizin in den letzten 15 Jahren erreicht, gemessen sowohl an der antepartalen Sterblichkeit, an der Neonatalsterblichkeit als auch an der Säuglingssterblichkeit. In Zahlen ausgedrückt bedeutet das zum Beispiel: von den Säuglingen, die 1980 verstarben, könnten nach dem heutigen Stand der Geburtshilfe und Neonatalmedizin ca. 70 % noch am Leben sein.
- Die Frühneonatalsterblichkeit konnte national und international zwischen 1975 und 1985 erheblich stärker reduziert werden als die Totgeburtlichkeit.

- Mit Ausnahme der sehr, sehr kleinen Frühgeborenen (unter 1 000 g) war die Totgeburtlichkeit im Beobachtungszeitraum 1980 bis 1995 immer größer als die Frühneonatalsterblichkeit.
- Der größere Rückgang der Frühneonatalsterblichkeit gegenüber der Totgeburtlichkeit setzte sich bis 1995 fort, allerdings in den einzelnen Geburtsgewichtsklassen recht unterschiedlich:
  - Frühsterblichkeit und Totgeburtlichkeit wurden bei den reifen Neugeborenen gleichmäßig reduziert. Zwei von 3 perinatal verstorbenen Kindern (69 %) waren Totgeburten.
  - Bei den Neugeborenen von 1 500–2 499 g kommen 1994 auf ein frühes Neonatal-Verstorbenes 4 Totgeborene (80 %). Während dieses Niveau bei den Neugeborenen von 2 000—2 499 g schon 1988 erreicht wurde, gelang dies bei den 1 500—bis 1 999 g-Kindern erst 1993/94. Entweder war die Bekämpfung der Totgeburtlichkeit in diesen Klassen weniger erfolgreich als die der Frühneonatalsterblichkeit oder es kommen durch den Fortschritt der Geburtshilfe immer neue Risikokinder nach.
- In den letzten 15 Jahren hat sich in der Schwangerschaftsüberwachung, dem Geburtsmanagement und der Neonatalversorgung viel verändert, wie z. B.:
  - die flächendeckende Einführung der Perinatalerhebungen mit einer Sensibilisierung der Geburtshelfer und Neonatalogen für die Frage nach Qualität und Qualitätsmanagement,
  - die 11 Novellen der Mutterschaftsrichtlinien mit der Einführung der Ultraschalluntersuchungen, der Untersuchungen der Hepatitis-Antikörper, der Anti-D-Prophylaxe etc., die zu den ersten, heute überall geforderten Leitlinien gehören,
  - die Intensivierung der Schwangerschaftsüberwachung, zu der auch die Schwangeren erheblich beigetragen haben,
  - der Siegeszug der Pulsoximetrie, der Surfactant- und der CPAP-Therapie in der Neonatalversorgung oder
  - die engere Kooperation zwischen ambulant und stationär tätigen Geburtshelfern und Neonatologen.
- Auch für die Geburtshilfe und die Neonatalmedizin gilt die alte Weisheit: daß der medizinische Fortschritt zwar dem einzelnen Patienten zu gute kommt, aber nicht immer der Bevölkerung. So hat die Zahl der sehr, sehr kleinen Frühgeborenen mit den hohen Risiken und den schlechteren Prognosen erheblich zu genommen, obwohl auch deren Prognose erheblich verbessert werden konnte.
- Zeitreihenvergleiche haben den Nachteil, daß sie nur mit großer Unsicherheit Schlüsse auf Kausalzusammenhänge zulassen. Hierfür wären größere Zahlen von Einzelfallanalysen zur Vermeidbarkeit von Totgeburtlichkeit und Frühneonatalsterblichkeit von Nöten.
- Die nach wie vor in Deutschland unterentwickelte Versorgungsforschung läßt das Erkennen eindeutig zuordenbarer Ursachen nicht zu, insbesondere dann nicht, wenn es sich um multifaktorielle Geschehen handelt.