THE INFLUENCE OF ANENCEPHALY UPON INTRAUTERINE GROWTH OF FETUS AND PLACENTA AND UPON GESTATION LENGTH

BY

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Summary
In order to determine the influence of anencephaly upon the intrauterine growth of fetus and placenta, and upon gestation length, 147 pregnancies with anencephaly were analyzed and compared with a control group.

There appeared to be a lower rate of intrauterine growth of the fetus and of the placenta in the anencephalic group. The birthweights of the anencephalic infants were much lower than those of the control group, but showed a steady increase which continued beyond term so that a birthweight level was achieved which was similar to that reached by the control group at term. The placentae of the anencephalic group showed a decreased weight in a high percentage of the cases, although this trend was less pronounced than for the birthweights.

The mean gestation length was significantly shorter in the anencephalic group than in the control group. Spontaneously born anencephalics from pregnancies with no hydramnios had a mean gestation length which was not significantly different from that of the control group. The distribution over the maturity periods differed significantly, however, in the high percentage of prematurely and postmaturely born anencephalic infants.

Short gestation length in anencephaly, on the one hand, is not due solely to hydramnios or to maternal factors; absence of hydramnios, on the other hand, is not invariably associated with prolonged gestation. Our observations do not support the suggestion that the anencephalic fetus might be the human analogue to the hypophysectomized lamb, nor that the pituitary-adrenal axis, of importance in the initiation of labour in sheep, plays the same role in humans.

Intraterine growth of the human fetus depends upon many factors, which include stature and race of the parents, parity, smoking, sex of the fetus, placental factors and the presence of maternal disorders such as vascular disease and diabetes mellitus (Gruenwald, 1966; Kloosterman, 1966; Thomson et al., 1968). Animal experiments show that intraterine growth and gestation length may in addition be influenced by neuroendocrine factors in the mother and in the fetus itself (Knobil and Caton, 1953; Heggestad and Wells, 1965; Liggins et al., 1967; Lincoln, 1970).

Similar experimental studies are out of the question in humans and so we depend upon comparisons between normal and pathological pregnancy for information.

In order to determine the possible role of the human fetal hypothalamus in the regulation of intraterine growth of the fetus and the placenta
and of gestation length, we therefore made an analysis of the effect upon those processes of anencephaly—a condition in which the fetal hypothalamus is either disturbed or absent and in which there are serious associated neuroendocrine disorders (see review by Eguchi et al., 1969).

**Patients, Methods and Definitions**

In the present study 147 pregnancies with anencephaly of the fetus are described. The patients were seen between 1931 and 1972 at the University Obstetric Clinic of the Wilhelmina Gasthuis in Amsterdam. Included in the study were 16 patients with an anencephalic fetus who attended the Training School for Midwives in Amsterdam between 1948 and 1957. "Anencephaly" is defined as a state in which the cranial vault is completely or almost completely missing, and in which the cerebral tissues are composed of small, irregular masses or vascular structures only (Potter, 1952; Hamersma, 1966).

**"Slight" and "severe" hydramnios**

The term "severe hydramnios" was used for the patients with a tense abdomen, non-palpable fetal parts and an inaudible fetal heart in whom an attempt was made to measure the volume of amniotic fluid that escaped when the membranes ruptured. To qualify for a diagnosis of "severe hydramnios" at least 2000 ml. of amniotic fluid had to be collected.

"Slight hydramnios" was the term used for patients in whom a slight excess of amniotic fluid was noted but in whom no attempt was made to measure the volume of amniotic fluid that drained when the membranes ruptured.

**Pre-eclampsia**

We define mild pre-eclampsia as an increase in maternal weight of 1500 to 2000 g. during a period of three weeks and/or a rise of blood pressure to 130/80 mm. Hg on at least two consecutive occasions. Moderate pre-eclampsia is an increase in maternal weight of 2000 to 3000 g. in three weeks and/or a rise of blood pressure to 140/90 mm. Hg on two consecutive occasions and/or the appearance of 1 g. or more of proteinuria per day. Severe pre-eclampsia means an increase in weight of at least 3000 g. in three weeks, a blood pressure of 150/100 mm, Hg and/or the excretion in urine of more than 1 g. of protein per day.

**Birthweight**

Infants were weighed almost immediately after birth. The birthweights of the anencephalic infants were plotted against the "normal growth course" which Kloosterman (1970) obtained from a group of 80,000 pregnancies studied during a similar period and in the same clinics. Like Kloosterman (1970) we did not include 4 sets of twins or 15 fetuses with third degree maceration which had died in utero at least three days before delivery. In addition, four fetuses given intrauterine injections (Honnebier, 1971, 1972; Honnebier and Swaab, 1973) were excluded. The birthweight of two anencephalic infants (one of 28 and one of 36 weeks maturity), could not be found in the records, so that a total of 122 birthweights was available for our study.

To allow for the fact that the low weight of anencephalic infants might, in part, be due to the absence of brain tissue, we subtracted the mean brain weight from the 50th percentile line of the control group. For this purpose we used the brain weights reported by Gruenwald (1963) between 28 and 43 weeks of pregnancy because his birthweight curve differed only slightly from that of Kloosterman (1970). The regression line of the birthweights of the anencephalic infants born between 28 and 54 weeks was calculated for the whole group, and for boys and girls separately, by the method of the least squares (De Jonge, 1963a).

**Placental weight and placental index**

The curves of placental weight and placental index (placental weight divided by fetal weight) were also compared with the "normal" curves which Kloosterman (1970) obtained in a group of 30,000 pregnancies. The cord was allowed to bleed and was then cut flush with the placenta, after which the membranes were trimmed down to the placental edge. All blood clots were removed from the placenta which was then placed in a four per cent formalin solution and weighed within a week on a balance which was accurate to 10 g. This procedure, also followed by Kloosterman (1970), appeared to cause a six per cent change in the weight of the fresh placenta (n = 13; SEM = 1 per cent).
Except for one case in which the placenta was processed as just described, we could not use data about placental weight obtained between 1931 and 1957 in the University Clinic because the placentae were, at that time, weighed together with part of the umbilical cord and the membranes (see Kloosterman, 1970). Because of this only 55 placental weights could be used for our study. The regression line of the placental weights of the anencephalic infants born between 30 and 50 weeks of pregnancy was calculated by the method of the least squares. The data for birthweight, placental weight and placental index of Kloosterman’s material are each divided into ten groups by means of nine centile lines (Kloosterman, 1970). The data about the pregnancies complicated by anencephaly were also placed into these ten groups. Like Kloosterman (1970), we placed the values that were situated exactly on a centile line into the group below. Comparisons were made between the distribution of values over the ten centile groups in pregnancies complicated by anencephaly and in “normal” pregnancies and the differences were analyzed by means of the $X^2$ test (De Jonge, 1963c).

Results

In the University Clinic the incidence of anencephaly between 1931 and 1973 was 1.7 per thousand. In 1971 the frequency was 0.6 per thousand (C.B.S., 1972) in the Netherlands.

Six women had a previous anencephalus, one of them with a different partner. Two women had each had two previous anencephalic infants. Five women had a previous child with a serious malformation of the central nervous system.

Table I gives clinical details of the 147 cases. In one case the sex of the newborn was not mentioned in the records. An autopsy was performed in 61 cases. In 28 infants macroscopic brain mass was visible. In all cases histology showed these masses to be haemorrhagic, oedematous and only partly composed of brain tissue. The adrenal glands were always hypo-plastic, regardless of birthweight or gestation length.

Hydramnios

A diagnosis of severe hydramnios was made at times which ranged from 24 to 37 weeks of pregnancy. In this group were three of the patients with twins, one of the patients whose infant was born after receiving intrauterine injections and four patients in whom hydramnios persisted after intrauterine death of the fetus of more than three days.

In six patients delivered at term the interval between the clinical detection of severe hydramnios and delivery was 6 to 11 weeks (mean 9.5 weeks), while the amount of amniotic fluid collected during parturition was 2 to 8 litres (mean 4.5 litres). In one case of severe hydramnios a carbon suspension was injected into the amniotic cavity on the day of delivery. At autopsy carbon particles were found in the digestive tract but not in the lungs of the infant. In six cases of severe hydramnios, the amniotic fluid contained meconium. At autopsy meconium was found in the lungs only (two infants), in the digestive tract only (three infants) or in both (one infant). One anencephalic infant which lived for five days after delivery appeared to be unable to swallow, although there was no hydramnios during pregnancy. These cases suggest that
brain stem function in anencephaly cannot be correlated with the presence or absence of hydramnios.

Slight hydramnios was noted in 20 patients. The interval between the diagnosis of slight hydramnios and delivery was at least three weeks and in one case twelve weeks. In this group were three of the patients who gave birth to macerated fetuses and one of the patients who had twins.

**Pre-eclampsia and miscellaneous complications**

Pregnancy was complicated by pre-eclampsia in eleven patients. The condition was mild in four patients (2.7 per cent), moderate in six patients (4.1 per cent) and severe in one patient (0.7 per cent). The overall incidence of mild, moderate and severe pre-eclampsia in the annual reports of the University Clinic over the last 20 years were 30.0 to 40.8 per cent, 9.3 to 11.7 per cent and 2.4 to 4.3 per cent respectively.

There was one patient who was found to have mild diabetes during pregnancy. One patient had rhesus iso-immunization but although the cord blood showed a positive Coombs test, there were no signs of haemolytic disease at autopsy. There were four sets of twins in the series and 15 stillborn infants showed third degree maceration. In one case the child had died only one day before delivery. This case is placed in the group of macerated infants in Table I.

**Birthweight**

Mean birthweight of 122 anencephalics showed a steady increase with increasing gestation length (Figs. 1 and 2). The regression line for these data is: \( y = 97.1 \times -1869 \) (R). This line runs well below the level of the 50th centile line of the normal group, even after correction for the absence of brain (B). The regression line for 87 anencephalic girls is given by \( y = 86.5 \times -1517 \) and for 34 anencephalic boys \( y = 83.0 \times -1517 \).

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* Sex not mentioned in the record.
— 1222. At 40 weeks the mean birthweight of boys was thus 155 g. more than that of girls. The birthweight of anencephalic infants was in the lowest centile group of normal values in 60·3 per cent of cases (Fig. 5). The distribution of the anencephalic birthweights within centile groups differs highly significantly \( (\alpha < 0.0005) \) from the “normal” distribution.

**Placental weight and placental index**

Figure 3 shows the placental weight for 55 anencephalics. Except for nine cases all placental weights were below the 50th centile line. The regression line of the placental weights is \( y = 9.6 \times + 14 \) (Fig. 3). The largest proportion, 29·6 per cent of placental weights, was found in the 10th to 25th centile group of the normal values (Fig. 5). The distribution of the placental weights over the centile groups differed highly significantly \( (\alpha < 0.0005) \) from the “normal” distribution (Fig. 5). Figure 4 shows the placental

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147 64 83 88 20 113 34 23 92 31 1 101 45 4 68 63 11 1 4 73
Birthweight (grams) by gestation length for 122 anencephalics; 50th centile line of the control group (50); 50th centile line of the control group after subtraction of mean brain weight (B); regression line of the birthweight of the anencephalics (R).

index for 55 anencephalics. In 29.6 per cent of cases, the placental index was in the 90th to 95th centile group of the normal values. The distribution over the centile groups differed highly significantly (α<0.005) from the "normal" distribution (Fig. 5).

Twins were kept out of the groups mentioned above. However, one can see from Table II that the birthweight of the anencephalic infant was less than that of the normal infant in all four cases. In two cases (delivered at 35 and 37 weeks) information about the placenta was insufficient for our analysis. The placental weight and placental index of the other two cases was in accordance with the figures described for the anencephalics in singleton pregnancies.

**Table II**

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<td>♀ 1180 g. placenta 420 g. index 0.271</td>
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<td>35*</td>
<td>♀ 1200 g. placenta ±1/3</td>
<td>♀ 1660 g. placenta ±2/3</td>
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<td>37</td>
<td>♂ 1670 g. placenta 290 g. index 0.173</td>
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<td>37†</td>
<td>♀ 2560 g.</td>
<td>♀ 2590 g.</td>
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*This monochorial twin has been described by Honnebier (1964).
† Placenta not correctly weighed.

**Fig. 3**

Placental weight (grams) by gestation length. The curves are the smoothed centile lines of the control group (Kloosterman, 1970). The dots are the placental weights of 55 anencephalics. The broken line (R) is the regression line of the placental weights of the anencephalics.

**Gestation length**

The frequency histogram of the "normal" group (Fig. 6) shows a peak at 40 weeks, a mean gestation length of 39.6 weeks, and a skewness to the left. The distribution over the three maturity periods is given in Table III.
The peak in the frequency histogram of all the anencephalics is found at 36 weeks (Fig. 7a). The mean gestation length (36.6 weeks) is significantly shorter ($p < 0.001$) than that of the control group. The distribution of all the anencephalics over the maturity periods (Table III) differs significantly ($\alpha < 0.0005$) from that of the control group, in that the proportion of both premature and postmature deliveries was high for the anencephalics.

If one omits the stillborn infants with third degree maceration, the infants given injections in utero and the twins (Fig. 7b) and also omits all patients with induced labour (Fig. 7c) the mean gestation length is not significantly altered ($0.50 < p < 0.60$); nor is the distribution over the three maturity periods ($0.90 < \alpha < 0.95$). The mean gestation length (36.9 weeks) of the spontaneously born anencephalics (Fig. 7c) is significantly shorter than that of the control group ($p < 0.001$).

The spontaneously born anencephalics have been divided into three groups according to the amount of amniotic fluid (Figs. 8a, 8b and 8c; Table III).

The mean gestation length of the spontaneously born anencephalic infants with no hydramnios (39.7 weeks) is not significantly different from that (39.6 weeks) of the control group ($0.10 < p < 0.20$), although their distribution over the three maturity periods differs highly significantly ($\alpha < 0.0005$), there being a high percentage of prematurely and postmaturely born anencephalics.

Both the mean gestation length and the distribution over the three maturity periods of the spontaneously born anencephalics with no hydramnios differ highly significantly from those of the group of spontaneously born anencephalics with slight hydramnios ($0.01 < p < 0.02$ and $\alpha < 0.0005$).

The mean gestation length of the groups with slight and severe hydramnios was significantly shorter ($p < 0.001$) than that of the control group.

When the patients with slight and severe hydramnios were considered together their mean gestation length differed significantly ($0.01 > p > 0.005$) from that of the group of patients with an anencephalic fetus and no hydramnios.

The mean gestation length of the group with severe hydramnios does not differ significantly
from that of the group with no hydramnios nor from that of the group with slight hydramnios ($0.5 < p < 0.10$ and $0.40 < p < 0.50$). However, the distribution of the maturity periods for these three groups of patients with an anencephalic fetus differed highly significantly ($a < 0.005$).

**DISCUSSION**

The group of patients with an anencephalic fetus and the control group were quite comparable. There were none the less certain differences: only 43 per cent of the mothers of anencephalic infants were primiparae whereas this percentage increased from 43·9 to 52 per cent in the control group over the last 20 years, and complications of pregnancy such as pre-eclampsia were less in the anencephalic group.

In both the control group (Kloosterman, 1969) and in the anencephalic group with its preponderance of girls the birthweight of boys was about five per cent more than that of girls. Thus sex difference in birthweight seemed to be independent of fetal hypothalamic function.

Situations providing the same maternal condition for the anencephalic and control fetus, i.e. twin pregnancies with one anencephalic fetus, are rare. We found only eight cases in the literature with data of birthweights (for review see Hamersma, 1966) to add to our four cases plus one case of triplets in which one was an anencephalus (Kohler and MacDonald, 1972). In 11 of these 13 cases the birthweight of the anencephalic child was considerably less than that of its normal twin sibling. The converse was true in one case in the literature, and corrections for loss of brain weight gave a higher birthweight for the anencephalus in one patient (delivered at 37 weeks) in our series. The two exceptions may be explained by the great divergence in birthweight (up to 1100 g.) found even in identica-

**Fig. 7**

Frequency distribution of gestation length. (a) for all anencephalic infants; (b) for an "exclusive" group; i.e. omitting those with third degree maceration, those who had injections in utero, and twins (c) for those in the "exclusive" group born spontaneously.
twins (Kloosterman, 1966). Variation in birthweight must also be the explanation for the six cases in which birthweight lay above the corrected 50th centile line (Fig. 2), since the brain and adrenals were the same at autopsy as in the cases which lay under the lowest birthweight centile.

Although Kloosterman (1970) studied patients during a slightly different time period and although he did not exclude patients with abnormal pregnancies his "normal growth curve" forms an acceptable basis for comparison. The regression line of the birthweights of the anencephalics shows an increase of 97 g. per week. Those birthweights reached far beyond term are similar to those of the control group at term (Figs. 1 and 2). Growth in the control group was 143 g. per week (50th centile line). Thus the two groups showed obviously different growth velocities. This is in agreement with observations of Hoet (1969) and Milic and Adamsons (1969). We were unable to confirm the presence in anencephaly of two periods with different growth velocities as compared to the control group (Kučera and Doležalova, 1972), nor the observation by Milic and Adamsons (1969) that there are two different groups of anencephalics with regard to length of gestation (Figs. 1 and 7a).

In the anencephalic group the mean placental weight gain calculated from the regression line was 10 g. per week, whereas the mean weight gain in the control group was 14 g. per week between 30 and 47 weeks of pregnancy.

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**Fig. 8**

Frequency distribution of gestation length for anencephalic infants in the “exclusive” group, born spontaneously. (a) when there was no hydramnios (b) when there was slight hydramnios; (c) when there was severe hydramnios.
Kloosterman (1963) stated that labour will start at a particular placental index, and this is the case in the control group (Fig. 4). In the anencephalic group, however, most of the deliveries take place prematurely, even though the placental index was higher than in the control group and a subsequent decline in the placental index was observed (Fig. 4). According to Milic and Adamsons (1969) this decline was seen in the anencephalics with a normal amount of amniotic fluid. They suggested, like Kloosterman (1965), that in such circumstances the placental index, as in normal conditions, might be an important factor in the determination of gestation length. From our group of anencephalics with a normal amount of amniotic fluid only 14 placentae could be used for placental index calculations (4 premature, 4 term, 6 postmature). The mean placental index of these 14 cases lay on the 67th centile line, or the centile group to which 25 per cent of the control group belonged. That the placental index is an important factor in the determination of gestation length in those cases of anencephaly in which there is no hydramnios is a supposition that is not supported by our observations.

The high incidence of premature delivery of anencephalics (Table III), has been attributed to the existence of hydramnios (Kloosterman, 1965; Anderson et al., 1969, 1971; Milic and Adamsons, 1969). In our material, however, a high incidence of premature deliveries was also found in the group of patients with no hydramnios (Table III). Moreover, in the group of patients with slight hydramnios the mean gestation length was even shorter than in the group of patients with severe hydramnios. In addition, severe hydramnios was noted for prolonged periods before the onset of labour. Although estimates of the amount of amniotic fluid are not very reliable, the presence of hydramnios only partly explained the premature delivery of anencephalics. That patients with slight and severe hydramnios formed separate groups is suggested by the fact that the time at which the excess of amniotic fluid was detected was similar for both groups. The mean maturity at which the diagnosis was first made was 30.3 weeks (SEM = 0.45; n = 50) for the patients with severe hydramnios whereas it was 29.8 weeks (SEM = 0.82; n = 14) for patients with only slight hydramnios. Another indication for two separate groups, beside gestation length, is the finding that in spite of the high placental index, the incidence of fetal death during parturition in the group with severe hydramnios was 65 per cent while it was 20 per cent in the patients with slight hydramnios; the number of female infants
each group was 73 per cent and 75 per cent respectively. This high incidence of fetal death in one of severe hydramnios was also noted by Eric and Adamsons (1969). With no hydramnios the incidence of fetal death during parturition was 35 per cent and 61 per cent of the infants were female.

It has been suggested that in the absence of hydramnios anencephaly would almost invariably be associated with prolonged gestation. Lack of fetal pituitary-adrenal activity is supposed to be responsible for the delay of the set of labour (Anderson et al., 1969 and 1971; Turnbull and Anderson, 1969). However, our group of patients with anencephalics and no hydramnios showed a mean gestation length similar to that of the control group (table III), though with a large range. Moreover, all cases from this group in which an autopsy was performed (5 premature, 5 term and 5 post-term infants) the adrenals were hypoplastic. The fetal zones were very atrophic and were sent in one case (34 weeks), where the adrenals weighed 100 and 120 mg. respectively. No relationship between the size of the renal cortex and gestation length could be demonstrated. None of our observations support the suggestion made by Anderson et al. (1969) and Turnbull and Anderson (1969) that the anencephalic fetus might be the analogue of the hypophysectomized lamb, and that the uterine-adrenal axis (of paramount importance the initiation of labour in sheep: Liggins et al., 67; Liggins, 1968 and 1969) might play a role in the initiation of labour in the human.

Our study raised questions about the cause of the decreased placental and fetal weights, and the alteration in fetal growth lociity produced by anencephaly. Animal experiments may give some of the answers. Rats showed that removal of the fetal brain reduced the sort of decrease in weight of the acenta and fetus which has been observed in man pregnancy complicated by anencephaly.

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