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## Histological characteristics of singleton placentas delivered before the 28th week of gestation

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### Summary

**Aims**—The placenta is a record of the fetal environment and its examination may provide information about the baby's subsequent growth and development. We describe the histological characteristics of 947 singleton placentas from infants born between 23 and 27 weeks gestation.

**Methods**—Consent was obtained from mothers who delivered before 28 weeks (clinical estimate). We evaluated the gross and histopathological features of the placenta and assessed pair-wise correlations between variables.

**Results**—Lesions of uteroplacental circulation (abruption, extensive infarction or thrombosis, marked basal or perivillous fibrin deposition, increased syncytial knots) were inversely related to those associated with inflammation of the membranes and cord. Earlier age favoured inflammatory variables, while older age favoured characteristics attributed to impaired blood flow. We observed



inflammation of the chorionic plate in 43%, the cord in 19%, and of chorionic plate vessels in 30%. Of the placentas with umbilical cord inflammation, 8% had no inflammation of the chorionic plate.

**Conclusions**—This study population is unique in its size and recruitment by gestational age rather than birth weight. Inflammation occurred frequently, but not in placentas that had characteristics of vasculopathy. The prevalence of inflammation decreased with increasing gestational age, while vasculopathy increased. Funisitis need not be accompanied by chorionic inflammation.

## Keywords

Chorioamnionitis; prematurity; placenta; histology

## INTRODUCTION

The incidence of preterm births is on the rise, partly due to the use of assisted reproduction technologies.<sup>1</sup> In the United States, 11% of births in 2005 occurred preterm with 2% under 32 weeks gestation,<sup>1</sup> and associated short and long term morbidity is estimated to produce a minimum socioeconomic burden of \$26.2 billion, or \$51 600 per infant born preterm.<sup>3</sup>

The three general clinical presentations of preterm birth are spontaneous preterm labour with intact membranes (40–50%), spontaneous preterm prelabour rupture of membranes (3–40%), and medical/surgical intervention because of a maternal or fetal indication (20%).<sup>4</sup> Clinical and laboratory evidence suggest that a number of pathogenic processes can lead to a final common pathway of preterm labour and delivery. Placental findings can sometimes resolve the underlying cause such as ascending bacterial invasion (i.e., chorioamnionitis), uteroplacental vasculopathy (e.g., pre-eclampsia) and abruption/haemorrhage.

We describe the gross and histological characteristics of placentas from a population of singleton live-born infants delivered before the 28th post-menstrual week. We discuss the interrelationships between variables related to chorionic plate and umbilical cord inflammation and vascular insufficiency as well as relative trends in these variables with gestational age.

The incidence of placental abnormalities in extreme prematurity is not well characterised since enrolment in most studies has been based on clinical parameters or birth weight that lead to an over-representation of growth-retarded babies.<sup>5</sup> This study offers the advantages of a large population and patient selection based on early gestational age.

## MATERIALS AND METHODS

### Population

The placentas were collected as part of a study designed to identify factors that increase risk for structural and functional neurological disorders in extremely low gestational age newborns (ELGANs). With approval of the individual institutional review boards, women delivering before 28 weeks gestation at one of 14 participating institutions were asked to enrol in the study. The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14<sup>th</sup> week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period (LMP) without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

The enrolment period covered years 2002–2004. A total of 1250 mothers of 1506 infants consented (an estimated 260 mothers were missed or declined to participate) but only 1411 placentas were submitted for pathological evaluation (totals refer to the number of umbilical



cords; i.e., twins are counted as two placentas). The 947 placentas from singletons are described here.

### Placental examination

Placentas were examined grossly by the available pathologist, often a resident, within 24 hours of delivery. Gross parameters recorded included trimmed weight, disc dimensions, the presence of an accessory lobe and membrane insertion (marginal, circummarginate, circumvallate). The cord was described with respect to insertion, twist, knot or pseudoknots and number of vessels. The disc parenchyma was examined and coded for focal lesions including infarcts, intervillous thrombus, retroplacental haematoma and vascular thrombosis. All other lesions were described in a free text section.

Histological examination of the placenta was performed following College of American Pathologists guidelines.<sup>6</sup> Representative sections were taken from all abnormal areas, as well as routine sections of the umbilical cord and a membrane roll, and two full thickness sections from the centre and a paracentral zone of the placental disc.

After the creation of a manual with definitions and illustrations, and completion of consensus case exercises to minimise observer variability, a pathologist at each site examined the slides for the histological characteristics listed on the ELGAN study data form (available on request).

Infarcts and intervillous fibrin, fetal stem vessel thrombosis, and decidual haemorrhage and fibrin deposition consistent with abruption were coded as present or absent. So, too, was the presence of decidual vasculopathy, absence of villous oedema, chorioangioma and chorioangioma. Vascular lesions were not quantified (i.e., number and size of infarcts). Chorionic villi were scored for subjective increase in syncytial knots.

Inflammation of the membranes was described in detail. At the chorionic plate of the disc, acute inflammation was assigned a stage from 0 to 3 (0, none; 1, neutrophils collecting in subchorionic space; 2, neutrophils into chorionic plate; 3, neutrophils up to amnionic epithelium). The severity of inflammation at the plate was assigned a grade from 1 to 3 (1, 1–9 neutrophils/20×; 2, 10–19 neutrophils/20×; 3, >20 neutrophils/20×). Inflammation of the free membranes (chorion/decidua) was graded from 0 to 4 (0, none; 1, single focus of 5–10 neutrophils; 2, several small foci or single focus of >10 neutrophils; 3, numerous large or confluent foci; 4, necrotising). Inflammation in the amnion was similarly but separately graded from 0 to 4.

The fetal inflammatory response was gauged by inflammation in the umbilical cord which was graded from 0 to 5 (0, none; 1, neutrophils within the inner third of one umbilical vessel; 2, neutrophils within the inner third of at least two umbilical vessels or through the wall of one vessel; 3, neutrophils in perivascular Wharton's jelly; 4, inflammation extending deep into Wharton's jelly; 5, 'halo lesion' ring of precipitate in Wharton's jelly encircling each vessel). Neutrophilic and eosinophilic infiltration into fetal stem vessels in the chorionic plate was also noted as present or absent.

Other lesions specifically noted as present or absent included subamniotic haematoma, maternal floor infarction, maternal sickle cells, trophoblast inclusions, chronic villitis, intervillitis, acute villitis, fibromuscular sclerosis (muscular hypertrophy with lumen obliteration), obliterative endarteritis (encroachment of lumen by subendothelial expansion associated with trapped red blood cells), placenta accreta and infectious agents.



## Pathologists

At most of the study institutions, the participating pathologist had a special interest in reproductive pathology. The pathologists helped in the development of the procedures manual and definitions as well as in the design of the data collection form. Placentas were processed as part of the daily workflow of the departments and then were reviewed by the ELGAN pathologist.

We did not conduct a central review of the histology. Each pathologist was provided with an illustrated manual of the characteristics and scoring systems as described. Fourteen sets of slides from 13 placentas were circulated among the pathologists for evaluation using the data form. Responses were summarised for the group and discussed by e-mail.

Once the study data were collected, we assessed observer variability by comparing among pathologists the rate of diagnosis for each data-form element. This approach assumes that the placentas at each institution are similar to the placentas at other institutions, and that much of the variability among institutions reflects the tendency of the pathologist at that institution to see each histological feature (Table 1). Since the study entry criteria were the same across institutions, this assumption seemed reasonable.

The pathologists were generally consistent in their use of diagnoses. The measures of inflammation were similar across institutions. Infarction and fetal vessel thrombosis were consistent with one outlier in each. Quantitation of syncytial knots, decidual haemorrhage and intervillous fibrin deposition are difficult to standardise<sup>7,8</sup> and pathologists fall into two groups, conservative and more liberal.

## Analysis

The data were entered into a central database and analysed using Stata Release 9.2 (2007; StataCorp, USA) statistical software. The  $\chi^2$  test for linear trend was used to evaluate trends with gestational age. Fisher's exact test was used for pair-wise comparisons of the histological characteristics.

## RESULTS

A total of 947 singleton placentas were evaluated (Table 2). Chorioamnionitis was the most frequent finding with inflammation of the chorionic plate in 43%, neutrophilic infiltration into fetal vessels of the plate in 30%, and inflammation of the cord in 19%. Morphological features associated with poor utero-placental perfusion including infarcts, increased syncytial knots and decidual haemorrhage suggesting abruption were each seen in about 20% of placentas.

Several histological characteristics varied with gestational age (Table 2). The frequency of inflammation in the chorionic plate and inflammation of the free membranes decreased with increasing gestational age. On the other hand, inflammation in the umbilical cord did not vary substantially with gestational age. 'Decidual haemorrhage suggesting abruption' decreased with increasing gestational age. Increased syncytial knots, however, were more common later in gestation, as were infarcts, even when placentas from the outlier institution (Table 1, institution H) were excluded. Fetal vascular thrombosis is uncommon in this gestation period and no trend with gestational age was apparent.

Relationships among histological characteristics are presented (Table 3). Inflammation in the cord, chorionic plate, and free membranes (chorion/decidua) occurred in the same placentas more commonly than would be expected by chance. Histological characteristics presumed to reflect poor utero-placental perfusion, including infarct (both with and without data from outlier institution H), syncytial knots and intervillous fibrin also clustered. By and large,



morphological features of each of these clusters tended to have an inverse relationship with features of the other. This was characterised by the observation that of all placentas that had increased syncytial knots, only 18% also had evidence of inflammation in the chorionic plate. Conversely, 50% of placentas that did not have increased syncytial knots had chorionic plate inflammation. Thrombosis of chorionic plate vessels showed only a modest tendency to occur in inflamed placentas.

A subset of placentas showed isolated umbilical cord inflammation without inflammation of the chorionic plate. Eight per cent of the placentas with umbilical cord inflammation of any grade had no inflammation of the chorionic plate. Similar findings have been observed in 5–8% of preterm and 17% of term placentas<sup>9</sup> and may represent under-sampling when histological chorioamnionitis does not involve the entire chorioamniotic plate.

## DISCUSSION

We have described placental histological characteristics of a large population of singletons born live before the 28<sup>th</sup> week of gestation. The value of this sample is its size and selection based on gestational age rather than clinical variables (e.g., pre-eclampsia) or birth weight.

The effect of weight versus age sample selection is illustrated by comparing our findings with those of Hansen, *et al.*<sup>10</sup> who recruited infants weighing less than 1501 g. With a median gestational age of 28.5 weeks, that population showed severe growth restriction in only 7% of those born at 26–28 weeks, but in 30% born after the 28<sup>th</sup> week.<sup>10</sup> In addition, in the Hansen study, 16% of infants had a birth weight more than two standard deviations below the mean for their gestational age, and 20% were born to mothers with pre-eclampsia. In contrast, only 7% of infants in our age selected population had birth weights more than two standard deviations below the mean for gestational age, and only 13% were born to pre-eclamptic mothers. Distortions related to birth weight sampling can lead to erroneous inferences about the prevalence of histological characteristics in placentas delivered much before term.

Chorioamnionitis is much more frequent in early gestation than at term. We observed inflammation of the chorionic plate in 43%, the chorionic plate vessels in 30%, and the cord in 19% of singleton placentas. In contrast, reported values at term for inflammation of the cord and chorionic plate in uncomplicated gestations are 1% and 4%, respectively.<sup>11,12</sup>

Our findings are compatible with smaller studies of early gestations; Hansen *et al.*<sup>10</sup> reported umbilical cord inflammation in 34% and chorionic vasculitis in 27% in very low birth weight infants. In our sample, 27% had chorionic plate vasculitis at 27 weeks. Salafia *et al.*,<sup>13</sup> reported umbilical inflammation/chorionic vasculitis in 38% of 28–32 week gestations, but with a very small sample size. The inverse relationship of inflammation with gestational age in gestations under 30 weeks has been described by others,<sup>14</sup> and does not seem to be present closer to term.<sup>10,13,15,16</sup>

We found that changes attributed to poor utero-placental perfusion were also more common in early gestation than at term. Our findings of infarcts in 20% and increased syncytial knots in 19% are a bit higher than in another gestational age-defined sample (22–32 weeks), which found infarcts in 13% of placentas, and increased syncytial knots in 11%.<sup>17</sup> On the other hand, in a birth weight-defined sample (< 1501 g), infarcts were seen in 17% of placentas, and increased syncytial knots were seen in 24%.<sup>10</sup> The higher rates in the birth weight-defined sample can be attributed, in part, to the over-representation of growth restricted fetuses/newborns, many of whom were products of a pre-eclamptic pregnancy. We base this inference on our finding that among the 13% of women in our sample who had pre-eclampsia, 54% had a placental infarct and 42% had increased syncytial knots, while among women who did not have pre-eclampsia, only 12% had a placental infarct and 14% had increased syncytial knots.



These findings support the view that the proportion of all placentas that are from pre-eclamptic pregnancies determines the prevalence of such histological correlates as infarcts and increased syncytial knots.

Studies of low birth weight<sup>10</sup> and early gestational age<sup>13</sup> placentas have consistently found placental features that are associated with inflammation and infection to cluster with one another, and histological characteristics attributed to utero-placental perfusion to cluster with each other.<sup>18</sup> Our data confirm these clusters and show a strong association between chorionic plate vasculitis, umbilical cord inflammation and thrombosis of chorionic plate vessels. We found a strong association between placental infarcts, increased syncytial knots and decidual haemorrhage/abruption. Placentas that had increased syncytial knots were considerably less likely to have inflammation than other placentas. Smaller series have noted a weak association between chorioamnionitis and abruption in third trimester singletons,<sup>19,20</sup> but we did not confirm that finding.

## CONCLUSION

This study population of infants born alive before 28 weeks gestation is unique in that the selection was by gestational age rather than birth weight, thereby reducing the impact of intrauterine growth retardation seen in birth weight defined samples. In this age group, the proportion of placental abnormalities is much higher than at term. In addition, the abnormalities generally fall into two non-overlapping subsets of either inflammation or vasculopathy. We also define a large group of placentas with isolated cord inflammation. This paper serves as a foundation for correlations with our clinical database, which includes microbiological findings, initiators of delivery, and perinatal outcomes.

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**Table 1**  
Percent of placentas with each histological characteristic according to each reader (column percents)

| Histological characteristic                 | Institution |    |    |    |    |    |    |    |    |    |    |    |    |    |      | #   |
|---|-------------|----|----|----|----|----|----|----|----|----|----|----|----|----|------|-----|
|   | A           | B  | C  | D  | E  | F  | G  | H  | I  | J  | K  | L  | M  | N  | Mean |     |
| Inflammation chorionic plate, stage 2-3     | 37          | 38 | 38 | 38 | 41 | 41 | 43 | 46 | 51 | 53 | 53 | 60 | 61 | 66 | 45   | 422 |
| Inflammation chorionic plate, grade 2-3     | 37          | 34 | 33 | 44 | 38 | 38 | 43 | 44 | 48 | 47 | 68 | 36 | 56 | 64 | 43   | 395 |
| Neutrophil infiltration fetal vessels plate | 30          | 30 | 16 | 32 | 34 | 30 | 30 | 32 | 36 | 22 | 22 | 38 | 22 | 44 | 30   | 272 |
| Inflammation free membranes, grade 3-4      | 35          | 44 | 31 | 45 | 33 | 42 | 50 | 52 | 46 | 42 | 68 | 40 | 39 | 62 | 43   | 404 |
| Inflammation umbilical cord, grade 3-5      | 8           | 23 | 11 | 9  | 26 | 25 | 30 | 13 | 20 | 19 | 19 | 19 | 17 | 27 | 19   | 172 |
| Infarct                                     | 19          | 11 | 22 | 9  | 20 | 14 | 12 | 80 | 9  | 8  | 19 | 21 | 18 | 11 | 20   | 184 |
| Increased syncytial knots                   | 16          | 9  | 8  | 29 | 26 | 5  | 42 | 7  | 41 | 22 | 29 | 9  | 17 | 16 | 19   | 183 |
| Intervillous fibrin                         | 16          | 35 | 32 | 74 | 8  | 5  | 7  | 78 | 6  | 3  | 11 | 10 | 24 | 11 | 24   | 227 |
| Decidual haemorrhage (abruption)            | 11          | 16 | 19 | 19 | 36 | 22 | 20 | 38 | 9  | 3  | 24 | 16 | 22 | 30 | 21   | 192 |
| Thrombosis of fetal vessels in plate        | 0           | 2  | 3  | 3  | 13 | 5  | 1  | 0  | 7  | 0  | 3  | 47 | 6  | 3  | 61   | 57  |



Percent of placentas with inflammation and vascular histological characteristics by gestational age in completed weeks (column percents)

Table 2

| Histological characteristic                        | Gestational age (completed weeks) |            |            |            |            |             |    | p value |
|--|-----------------------------------|------------|------------|------------|------------|-------------|----|---------|
|  | 23 n = 84                         | 24 n = 176 | 25 n = 197 | 26 n = 237 | 27 n = 253 | All n = 947 |    |         |
| Inflammation chorionic plate, grade 2-3, stage 2-3 | 65                                | 55         | 42         | 38         | 34         | 43          | 43 | ≤0.001  |
| Neutrophilic infiltrate fetal vessels of plate     | 42                                | 33         | 31         | 24         | 27         | 30          | 30 | 0.004   |
| Eosinophilic infiltrate fetal vessels of plate     | 12                                | 12         | 9          | 8          | 10         | 10          | 10 | 0.30    |
| Inflammation free membranes, grade 3-4             | 58                                | 52         | 47         | 37         | 36         | 43          | 43 | ≤0.001  |
| Inflammation in umbilical cord, grade 3-5          | 19                                | 20         | 23         | 18         | 17         | 19          | 19 | 0.30    |
| Infarct  | 13                                | 17         | 16         | 22         | 25         | 20          | 20 | 0.003   |
| Increased syncytial knots                          | 8                                 | 15         | 17         | 21         | 26         | 19          | 19 | ≤0.001  |
| Intervillous fibrin deposition                     | 29                                | 20         | 25         | 21         | 28         | 24          | 24 | 0.57    |
| Decidual haemorrhage (abruption)                   | 29                                | 21         | 22         | 20         | 17         | 21          | 21 | 0.03    |
| Thrombosis of fetal vessels in plate               | 4                                 | 9          | 6          | 3          | 8          | 6           | 6  | 0.88    |
| Cord insertion: marginal                           | 3                                 | 11         | 9          | 9          | 9          | 9           | 9  | 0.38    |
| Cord insertion: velamentous                        | 3                                 | 1          | 3          | 2          | 2          | 2           | 2  | 0.94    |
| Circumvallate insertion of membranes               | 0                                 | 3          | 1          | 5          | 3          | 3           | 3  | 0.11    |



Table 3

Co-occurrence of histological characteristics (column percents)

|  | Plate     |           | Neutrophil |           | Eosinophil |           | Membrane  |           | Umbilical cord |           | Infarct   |           | Increased syncytial knots |           | Decidual haemorrhage |           | Fibrin    |           | Thrombosis |           |
|--|-----------|-----------|------------|-----------|------------|-----------|-----------|-----------|----------------|-----------|-----------|-----------|---------------------------|-----------|----------------------|-----------|-----------|-----------|------------|-----------|
|  | Yes       | No        | Yes        | No        | Yes        | No        | Yes       | No        | Yes            | No        | Yes       | No        | Yes                       | No        | Yes                  | No        | Yes       | No        | Yes        | No        |
| Maximum <i>n</i>                                   | 356       | 465       | 272        | 650       | 92         | 830       | 404       | 525       | 172            | 727       | 104       | 754       | 183                       | 759       | 192                  | 743       | 227       | 701       | 57         | 864       |
| Inflammation chorionic plate, grade 2–3, stage 2–3 |           |           | <b>98</b>  | <b>19</b> | <b>99</b>  | <b>36</b> | <b>91</b> | <b>6</b>  | <b>98</b>      | <b>30</b> | <b>22</b> | <b>48</b> | <b>18</b>                 | <b>50</b> | 42                   | 44        | 35        | 46        | 54         | 42        |
| Neutrophil infiltrate fetal vessels of plate       | <b>52</b> | <b>1</b>  |            |           | <b>93</b>  | <b>23</b> | <b>63</b> | <b>4</b>  | <b>84</b>      | <b>17</b> | <b>17</b> | <b>33</b> | <b>12</b>                 | <b>34</b> | 28                   | 30        | 27        | 30        | 45         | 29        |
| Eosinophil infiltrate fetal vessels of plate       | <b>18</b> | <b>0</b>  | <b>32</b>  | <b>1</b>  |            |           | <b>21</b> | <b>1</b>  | <b>30</b>      | <b>6</b>  | <b>5</b>  | <b>11</b> | <b>6</b>                  | <b>11</b> | 10                   | 10        | 6         | 11        | 18         | 10        |
| Inflammation free membranes, grade 3–4             | <b>92</b> | <b>7</b>  | <b>93</b>  | <b>23</b> | <b>93</b>  | <b>38</b> |           |           | <b>94</b>      | <b>32</b> | <b>25</b> | <b>48</b> | <b>22</b>                 | <b>49</b> | 42                   | 44        | 38        | 45        | 44         | 43        |
| Inflammation umbilical cord, grade 3–5             | <b>46</b> | <b>1</b>  | <b>54</b>  | <b>4</b>  | <b>56</b>  | <b>15</b> | <b>41</b> | <b>2</b>  |                |           | <b>9</b>  | <b>21</b> | <b>7</b>                  | <b>22</b> | 18                   | 20        | 13        | 21        | 26         | 19        |
| Infarct  | <b>11</b> | <b>30</b> | <b>11</b>  | <b>23</b> | 10         | 20        | <b>11</b> | <b>26</b> | <b>9</b>       | <b>22</b> |           |           | <b>40</b>                 | <b>15</b> | <b>35</b>            | <b>16</b> | <b>42</b> | <b>12</b> | <b>25</b>  | <b>19</b> |
| Increased syncytial knots                          | <b>7</b>  | <b>35</b> | <b>8</b>   | <b>24</b> | 12         | 20        | <b>10</b> | <b>27</b> | <b>7</b>       | <b>22</b> | <b>39</b> | <b>15</b> |                           |           | 22                   | 19        | 21        | 19        | 18         | 19        |
| Decidual haemorrhage (abruption)                   | 21        | 19        | 19         | 21        | 21         | 20        | 50        | 21        | 19             | 21        | <b>36</b> | <b>17</b> | 23                        | 20        |                      |           | <b>30</b> | <b>17</b> | <b>25</b>  | <b>20</b> |
| Intervillous fibrin deposition                     | 20        | 28        | 21         | 24        | 13         | 25        | 21        | 26        | 16             | 26        | <b>52</b> | <b>17</b> | 26                        | 24        | 36                   | 21        |           |           | 18         | 24        |
| Thrombosis of fetal vessels in plate               | 7         | 5         | 9          | 5         | 11         | 6         | 6         | 6         | 8              | 6         | 8         | 6         | 6                         | 6         | 8                    | 6         | 5         | 6         |            |           |

Pair-wise associations were examined with Fisher's exact test and those significant at  $p \leq 0.001$  are indicated in bold.