

## Fetal haemoglobin Bart's disease in Hong Kong: why early diagnosis could not be made?

Pregnancies complicated by fetal haemoglobin (Hb) Bart's disease are associated with poor perinatal outcomes, which include: early onset of hydrops fetalis, intrauterine or early neonatal death, and a higher risk of maternal pre-eclampsia.<sup>1</sup> Even though there are case reports of survivors with or without intrauterine transfusion, postnatal regular transfusion is necessary until bone marrow transplantation can be successfully performed.<sup>2,3</sup> As a result, affected pregnancies are usually terminated (after counselling) and hence early prenatal diagnosis is of great value.

In Hong Kong, from July 2000 onwards, a universal antenatal screening and prenatal diagnosis programme for thalassaemia has been in operation at every public hospital and Maternal and Child Health Centre (MCHC).<sup>4</sup> This leads to a dramatic reduction in the prevalence of this condition.<sup>5</sup> Prior to this programme, the routine antenatal haematological blood tests in MCHCs did not include a complete blood count, just the Hb level.<sup>6</sup> As some thalassaemia carriers did not have a low Hb, screening depending on Hb level alone missed a proportion of cases and hence, fetal Hb Bart's disease was not uncommonly seen in late pregnancies or at delivery.<sup>7</sup> Nowadays, with the properly instituted screening programme, any pregnant women with a low mean corpuscular volume (MCV) will be followed up and their partner's MCV will also be checked. Thus, couples with  $\alpha$  thalassaemia traits undergo counselling regarding the possibility of serial ultrasound examination or invasive prenatal testing. In fetuses with Hb Bart's disease, anaemia occurs very early and hence signs of fetal cardiomegaly and placentomegaly may be detected on ultrasound from the second trimester onwards. Under experienced hands, serial ultrasound examination of the fetal cardiothoracic ratio and placental thickness (from 12 weeks onwards) should help to identify all cases of Hb Bart's disease prior to 24 weeks of gestation.<sup>8-10</sup>

In this issue of the journal, Kwan et al<sup>11</sup> present 59 cases of fetal Hb Bart's disease diagnosed between 1 January 2000 and 31 December 2009 in two of Hong Kong's tertiary obstetrics units. Of these, 13 (22%) were only diagnosed after 24 weeks of gestation. The perinatal mortality among these late presenters was 85%; only two survived but both had significant morbidities.<sup>11</sup> Mothers presenting late were more likely than early presenters to have abnormal symptoms or signs (85% vs 0%) and suffer

from gestational hypertensive disorder (54% vs 0%).<sup>11</sup> Hence, this paper re-confirmed the benefit of early diagnosis of this condition, which enabled affected women to make an early decision about termination of pregnancy, so as to avoid the associated complications in late gestation.

In the cases described by Kwan et al (see Table 2<sup>11</sup>), the reasons for not being able to achieve an early diagnosis could be summarised into three: (1) non-booking or late-booking status; (2) failure to recognise the risk and offer a prenatal diagnosis; and (3) non-paternity.

Late presentations were significantly associated with non-eligible obstetric patients (69% vs 11%) and non-booked status (62% vs 0%). In all, nine of the 13 cases were either non-registered with public or private sector facilities in Hong Kong before presentation (cases 8-13), or booked only after 24 weeks of gestation (cases 1, 2, and 5). For the non-booked women, the data did not allow an assessment of the degree of their antenatal care outside Hong Kong, if any. Notably, two of these six pregnancies involved the same woman (cases 10-11). During her second pregnancy, she did not have an early booking in Hong Kong and the diagnosis was missed again despite some form of ultrasound screening in China, after her first pregnancy had ended in a neonatal death due to Hb Bart's disease. Of the three who were booked late, two defaulted follow-up, and hence prenatal diagnosis could not be offered (cases 1 and 2). Another woman (case 5) presented at 30 weeks, and had the diagnosis established quickly at 32 weeks. In the latter case however, the diagnosis should have been made much earlier in China where she had her antenatal care, as both partners were known to have low MCVs. Hence, even with the availability of good antenatal services in Hong Kong, abstinence from local antenatal care until late gestation was the most important cause for the resurgence of late-presenting Hb Bart's disease.

Vigilance by the health care providers is always a crucial element in the successful implementation of any antenatal screening programmes. However, even in developed countries, service failure, including a failure to recognise the risk and offer a prenatal diagnosis, could still be demonstrated in over a quarter of affected pregnancies with thalassaemia.<sup>12</sup> This could be the reason for late diagnosis in two cases which were managed initially in the private sector in Hong Kong (cases 3 and 4

in Kwan et al's series<sup>11</sup>). One mother (case 4) had a low MCV, but regrettably her partner's MCV status was not checked. Another mother (case 3) was the one who underwent in-vitro fertilisation, where pre-implantation genetic diagnosis (PGD) was performed for fetal Hb Bart's disease. However, this diagnostic procedure performed on cell(s) removed from a pre-implanted embryo carries a small but known rate yielding false-positive and false-negative results.<sup>13</sup> Therefore, chorionic villus biopsy or amniocentesis is recommended to confirm such PGD findings.<sup>13</sup> Since amniocentesis was performed in this case for karyotyping, it is regrettable that presence of the  $\alpha$  gene was not checked.

In Kwan et al's series,<sup>11</sup> non-paternity was suspected in three instances (cases 6-8). This could well have been the reason for the missed diagnosis in early pregnancy in cases 6 and 7, as prenatal screening and diagnosis was not arranged for them because the putative partners' MCVs were normal. The authors excluded the rare possibility of any non-deletional  $\alpha$  gene abnormality in one of these partners. Another even rarer possibility is uniparental disomy, where the fetus has inherited both alleles of the chromosome 16 from the mother.<sup>14</sup> This possibility was also excluded (personal communication). Hence, non-paternity seemed very likely. The third case where non-paternity was suspected did not have an antenatal booking (case 8).

If we can identify the main reasons for re-emergence of late presentations of Hb Bart's disease, maybe we can find room for improvement. Hopefully, more public education to raise the awareness of the possibility of thalassaemia and the importance of early diagnosis can reach all couples who are planning a family. Apart from the lack of awareness of its importance, there could be many other reasons why pregnant women do not have regular antenatal care. However, given that many human decisions are based on a balance of risks, increased vigilance among women should increase the proportion opting for proper antenatal booking and screening. It is obviously difficult to influence the medical system across the border, but for sure, good antenatal screening and prenatal diagnosis programmes for thalassaemia are available among obstetrics units in China.<sup>10</sup> Increased vigilance among general obstetricians, both in Mainland China and in Hong Kong, is another crucial factor, which can only be achieved through continuous medical and professional education.

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