



## DYSBETALIPOPROTEINAEMIA — CLINICAL AND PATHOPHYSIOLOGICAL FEATURES

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**Objectives.** Dysbetalipoproteinaemia (type III hyperlipidaemia, broad-beta disease) is a highly atherogenic genetic disorder of lipoprotein metabolism. It presents with a severe mixed hyperlipidaemia in which the ratio of total cholesterol to triglycerides is typically 2:1. There is a high incidence of atherosclerotic complications and severe hypertriglyceridaemia may cause pancreatitis. Highly effective therapy is available and affected families also benefit from genetic counselling.

We present a review of our experience with dysbetalipoproteinaemia at the lipid clinic of Groote Schuur Hospital to enhance awareness of this serious condition, for which the index of suspicion should be raised.

**Design.** Retrospective review of case records, 1969 - 2001.

**Setting.** Lipid clinic of Groote Schuur Hospital, Cape Town.

**Subjects.** Patients with dysbetalipoproteinaemia diagnosed by the presence of cholesterol-enriched very-low-density lipoproteins (VLDL) and/or dyslipidaemia associated with homozygosity for apolipoprotein E2 or carriers of the apoE2 (Arg145→Cys) mutation.

**Results.** One hundred and five patients were identified, 55 of whom were male and 50 female. The age at presentation was  $48.8 \pm 11.1$  years (mean, standard deviation). Total cholesterol was  $12.0 \pm 5.5$  mmol/l and plasma triglycerides  $8.3 \pm 9.8$  mmol/l. The ratio (by mass) of cholesterol to triglycerides within VLDL was  $0.52 \pm 0.17$ , while VLDL cholesterol to plasma triglycerides was  $0.33 \pm 0.09$ . Fifty patients were  $\epsilon\epsilon$  homozygotes while 22 carried the apoE2 (Arg145→Cys) mutation. Palmar crease xanthomas occurred in 20% of patients, cutaneous xanthomas in 18%, and tendon xanthomas in 13%. Coronary artery disease was found in 47% of patients and peripheral vascular disease in 20%. Fibrates were the most commonly used hypolipidaemic agents (48%), while 31% of patients received combination therapy with a fibrate and statin. Statin monotherapy was used in 11% of patients and a few

patients were treated with niacin or required no drug therapy. The treated cholesterol was  $5.7 \pm 2.4$  mmol/l, with plasma triglycerides of  $2.7 \pm 1.9$  mmol/l.

**Conclusions.** Dysbetalipoproteinaemia is a highly atherogenic disorder and is extremely responsive to therapy. A significant proportion of dysbetalipoproteinaemia locally is caused by the apoE2 (Arg145→Cys) mutation and is therefore dominantly inherited. This mutation is particularly prevalent in the black community where dysbetalipoproteinaemia may be undiagnosed in many patients. Patients with severe mixed hyperlipidaemia or clinical stigmata of dyslipidaemia should be assessed at a lipid clinic for a specific diagnosis and initiation of therapy.

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The Groote Schuur Hospital lipid clinic is one of two tertiary referral lipid clinics in the Western Cape province of South Africa. Approximately 300 new patients with a wide variety of lipid disorders are seen every year. The clinic aims to make a specific diagnosis for every patient by taking a full family history, carefully examining for clinical signs of dyslipidaemia and by performing investigations that will further assist in the identification of monogenic (so-called 'major gene defects') disorders of lipid metabolism. Such disorders cause severe premature atherosclerosis in the absence of other risk factors<sup>1,2</sup> and require family screening so that early preventive therapy can be instituted.<sup>2</sup> Apart from the routine lipid profile comprising fasting triglycerides, total cholesterol, high-density cholesterol and calculated low-density cholesterol, additional investigations (electrophoresis, ultracentrifugation and genotyping) may be done as necessary to confirm or exclude diagnoses suspected clinically.

Dysbetalipoproteinaemia is a monogenic disorder of lipoprotein metabolism. It is caused by mutations that disrupt the binding of apolipoprotein E (apoE) to lipoprotein receptors. Although uncommon, with an estimated incidence of 1 - 5 per 5 000 in the USA,<sup>3</sup> it is an important disorder to recognise because of its extreme atherogenicity and the often very favourable response to therapy. Dysbetalipoproteinaemic patients have a mixed hyperlipidaemia, with elevation of both cholesterol and triglycerides. The ratio of cholesterol to triglyceride in the plasma is often around 2:1 in molar terms, but may be very variable. This disorder is also known as type III hyperlipidaemia, remnant removal disease, and broad beta disease or familial dysbetalipoproteinaemia.

Triglyceride-rich lipoproteins are synthesised in the gut as chylomicrons (CM) after a meal and by the liver as very-low-density lipoproteins (VLDL). Triglyceride-rich lipoproteins contain proportionally little cholesterol and their main function is to transport triglycerides in the blood. Endothelium-bound



lipoprotein lipase (LPL) hydrolyses some of the triglyceride content of circulating triglyceride-rich lipoproteins and smaller particles called remnants are formed. Remnants are subsequently taken up by the liver where they are further metabolised. The uptake of remnants by the liver is mediated through the low-density lipoprotein receptor (LDLR) and the low-density lipoprotein receptor-related protein (LRP) with heparan sulfate proteoglycans (HSPG) acting as a co-factor for LRP as well as mediating independent uptake of remnants.<sup>4,6</sup> ApoE is the ligand with which remnants bind to their hepatic receptors. Remnant particles acquire apoE in the circulation mainly through transfer of apoE from high-density lipoproteins (HDL). In dysbetalipoproteinaemia, binding of apoE to hepatic receptors is either defective<sup>3</sup> because of mutations in apoE, or rarely there is apoE deficiency. Fig. 1 gives a schematic representation of remnant metabolism.

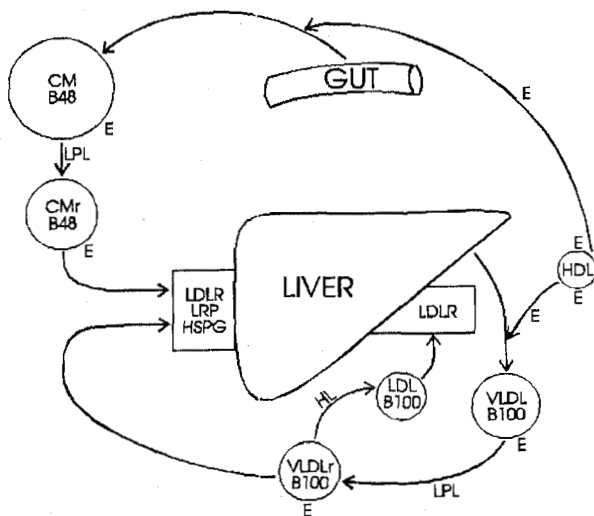


Fig. 1. Schematic representation of remnant lipoprotein metabolism. Chylomicrons (CM) from the gut and hepatic VLDL undergo triglyceride hydrolysis by lipoprotein lipase (LPL) and chylomicron remnants (CMr) and VLDL remnants (VLDLr) are formed. VLDLr can be converted to LDL by hepatic lipase (HL) or can be taken up directly by the liver as is the case with CMr. ApoE mediates binding of remnants to hepatic lipoprotein receptors. The hepatic lipoprotein receptors are the LDL receptor (LDLR), the LDL receptor related protein (LRP) and heparan sulfate proteoglycans (HSPG).

At the apoE gene locus three common variants designated  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$ <sup>28</sup> are found, resulting in three homozygous ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 3/\epsilon 3$ ,  $\epsilon 4/\epsilon 4$ ) and three heterozygous ( $\epsilon 2/\epsilon 3$ ,  $\epsilon 2/\epsilon 4$ ,  $\epsilon 3/\epsilon 4$ ) genotypes. The apoE encoded by the three common genotypic variants is designated apoE2, E3 and E4. The majority of the population has an apoE3/E3 phenotype, while about 1% of the population is homozygous for apoE2. ApoE2 homozygosity is the commonest molecular cause of dysbetalipoproteinaemia, making the inheritance recessive. There are, however, other apoE mutations that are dominantly

expressed such as the apoE2 (Arg145→Cys) mutation. In apoE2 homozygotes remnants bind poorly to hepatic receptors<sup>9</sup> with delayed clearance from the circulation, but under ordinary circumstances their removal is still sufficient to avoid hyperlipidaemia. Any stress of the system, by either overproduction (diabetes, alcohol, obesity) of triglyceride-rich lipoproteins, decreased receptor expression (hypothyroidism) or impaired lipolysis (renal failure) could precipitate hyperlipidaemia. Age is a powerful permissive factor for dysbetalipoproteinaemia in genetically predisposed individuals — there is a delayed penetrance of the phenotype so that hyperlipidaemia usually presents in adulthood. It is very unusual to see hyperlipidaemia in premenopausal females, in whom oestrogen is protective by enhancing remnant clearance.<sup>10</sup> Hyperlipidaemia in dysbetalipoproteinaemic patients not only results from impaired remnant clearance, but accumulation of abnormal apoE impairs lipolysis of triglycerides in VLDL by LPL,<sup>11,12</sup> reduces the activity of hepatic lipase<sup>13</sup> and stimulates the production of VLDL by the liver.<sup>14</sup>

Dysbetalipoproteinaemia can be diagnosed on clinical grounds if the characteristic palmar crease xanthomas (yellow discolouration of palmar creases) are seen in the presence of a mixed hyperlipidaemia (Fig. 2). Patients may also have tuberous, tubero-eruptive and tendon xanthomas, but these lesions are not unique to dysbetalipoproteinaemia and are frequently absent (Fig. 3). Laboratory confirmation requires specialised testing, but there are no universally accepted diagnostic criteria. Testing is based either on analysis of apoE, usually by genotyping, or on analysis of lipoproteins for their composition or electrophoretic properties. Only 42% of patients have the characteristic broad-beta band on agarose gel electrophoresis,<sup>15</sup> which is the most widely available test. Electrophoresis of ultracentrifugally isolated lipoprotein fractions and the demonstration of abnormally migrating VLDL ( $\beta$ -VLDL) is diagnostically more useful. The presence of  $\beta$ -migrating lipoproteins in the VLDL fraction (VLDL



Fig. 2. Palmar crease xanthoma. Yellow infiltration of the palmar creases is diagnostic of dysbetalipoproteinaemia.

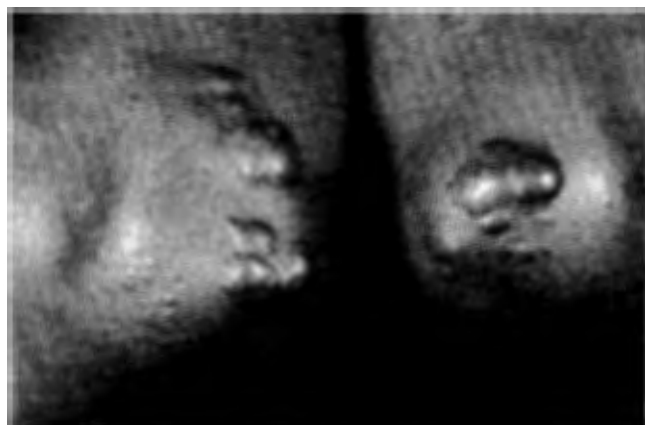


Fig. 3. Tuberous xanthoma. Large tuberous xanthoma on the elbows. Complete regression was seen on therapy.

lipoproteins normally migrate into a pre- $\beta$  position) explains the name of this condition. Dysbetalipoproteinaemic patients have cholesterol-enriched VLDL and abnormally high ratios of VLDL cholesterol compared with either VLDL or plasma triglycerides. Mass ratios of either 0.42<sup>16</sup> or 0.35<sup>17</sup> have been suggested as diagnostic ratios within VLDL, while 0.30<sup>18</sup> or 0.25<sup>19</sup> are the proposed criteria when comparing VLDL cholesterol with plasma triglycerides. All these tests require ultracentrifugation, which is available only in research laboratories. The diagnostic accuracy is reduced if hyperlipidaemia is only mild or extremely severe.<sup>16-19</sup> The common apoE alleles are determined by polymerase chain reaction (PCR) and restriction fragment length analysis,<sup>20</sup> while apoE phenotype can be determined by one of several isoelectric focusing techniques.<sup>21</sup>

## METHODS

We retrospectively reviewed the records of all dysbetalipoproteinaemic patients identified by review of the clinical and laboratory databases. VLDL composition was analysed after fasted EDTA plasma was adjusted in density with potassium bromide and underlayered below a saline/EDTA cushion. Ultracentrifugation was performed for 16 hours in a Beckman SW40 rotor at 100 000 g. The supernatant was recovered and lipid concentrations were analysed using standard enzymatic methods. All ratios are expressed in terms of mass. ApoE genotyping was performed according to a previously reported method.<sup>20</sup> Clinical information was incomplete on some patients seen before 1985. We based the diagnosis of dysbetalipoproteinaemia on the presence of one of the following criteria: (i) a mixed hyperlipidaemia (total cholesterol > 7 mmol/l and plasma triglycerides > 3 mmol/l) with a ratio of cholesterol in VLDL to triglyceride in VLDL of  $\geq 0.42$  or a ratio of cholesterol in VLDL to plasma triglyceride of  $\geq 0.30$ ; and (ii) a mixed hyperlipidaemia associated with

homozygosity for  $\epsilon 2$  or the presence of one of the other apoE mutations associated with dysbetalipoproteinaemia.

Continuous variables are given as mean  $\pm$  standard deviation (SD), and significance was tested using the unpaired *t*-test or Fisher's exact test. A *P*-value < 0.05 was taken as statistically significant.

## RESULTS

We identified a total of 105 patients who fulfilled the above criteria. Our first patient was diagnosed clinically in 1969 but the diagnosis has subsequently been confirmed by ultracentrifugation and genotyping. Follow-up on the 91 patients who returned at least once to the clinic after their initial consultation represents approximately 490 patient-years.

The reasons for referral to the lipid clinic are listed in Table I. Most patients with cutaneous xanthoma were initially referred to dermatologists. Other modes of presentation included symptomatic atherosclerotic disease, incidental discoveries and pancreatitis. Patients are further characterised in Table II according to the clinical features at presentation.

Table I. Indication for referral of patients with dysbetalipoproteinaemia to the lipid clinic

Indication	N (%)
Secondary prevention	45 (43)
Incidental finding of hyperlipidaemia, screening	39 (37)
Cutaneous xanthomas	12 (11.5)
Hypertriglyceridaemic pancreatitis	4 (3.8)
Family screening	3 (2.8)
Insufficient data	2 (1.9)

Dysbetalipoproteinaemia occurred in all racial groups. We diagnosed dysbetalipoproteinaemia in 11% of all black patients referred to the lipid clinic, making this diagnosis the commonest genetic hyperlipidaemia seen in this population group at our clinic.

We found palmar crease xanthoma in 21/101 patients (20%), and 12 of 21 patients (57%) with palmar crease xanthomas also had tuberous and/or tubo-eruptive xanthomas. Seven patients had cutaneous xanthomas without palmar crease infiltration. Lipid deposition in the skin regressed with effective lipid-lowering therapy in all our patients. Thirteen patients (13%) had tendon xanthomas, found exclusively in the Achilles tendons. Clinical stigmata of dyslipidaemia were found with comparable frequency in both sexes.

Of 101 patients for whom sufficient clinical data were available, 37 (37%) had evidence of ischaemic heart disease (IHD) at presentation as witnessed by a convincing history of angina pectoris, previous myocardial infarction, coronary artery bypass surgery in the past or percutaneous coronary revascularisation. During follow-up another 10 patients were



Table II. Clinical characteristics of dysbetalipoproteinaemic patients at the lipid clinic

	Males	Females	Total	P-value
<b>Age</b>				
Number of patients	55	50	105	
Mean age at presentation ( $\pm$ SD)	46.3 (10.6)	51.6 (11.4)	48.8 (11.1)	0.015
Age range (years)	6 - 65	22 - 80	6 - 80	
<b>Lipid values</b>				
Number of patients	55	50	105	
Presentation TC (mmol/l)	11.9 (5.9)	12.0 (4.8)	12 (5.5)	NS
Presentation TG (mmol/l)	9.2 (11.1)	7.3 (7.8)	8.3 (9.8)	NS
Number of patients	45	39	84	
Best TC (mmol/l)	5.5 (2.0)	6.1 (2.7)	5.7 (2.4)	NS
Best TG (mmol/l)	2.8 (2.2)	2.5 (1.5)	2.7 (1.9)	NS
<b>Secondary causes</b>				
Number of patients	55	46	101	
Diabetes (N)	17	17	34	NS
Hypothyroidism (N)	1	3	4	NS
Renal disease (all) (N)	2	5	7	NS
Alcohol (N)	4	0	4	NS
<b>Complications</b>				
Number of patients	55	45	100	
IHD	25	22	47	NS
PVD	5	15	20	0.005

SD = standard deviation; TC = total cholesterol; TG = triglycerides; IHD = ischaemic heart disease; PVD = peripheral vascular disease; NS = not statistically significant,  $P > 0.05$ .

diagnosed with IHD, resulting in a prevalence of 47%. Twenty patients (20%) had peripheral vascular disease diagnosed based on claudication and abnormalities on clinical examination or a history of surgery for obstructive peripheral vascular disease. Peripheral vascular disease was found significantly more frequently in females than males.

Co-morbidity is frequent in patients with dysbetalipoproteinaemia. The prevalence of diabetes was 34%, and 55% of patients were hypertensive. Hypothyroidism was identified in four patients and hyperlipidaemia improved markedly on replacement therapy with thyroxine. In 4 patients there was significant alcohol abuse, while 2 patients had the nephrotic syndrome. Another 5 patients had significant other renal disease.

The mean total cholesterol at presentation was  $12.0 \pm 5.5$  mmol/l with a maximum of 34.3 mmol/l. Plasma triglycerides had greater variability with a mean of  $8.3 \pm 9.8$  mmol/l (median 5.1 mmol/l) and a maximum of 63.2 mmol/l. Ultracentrifugal data are available for 104 patients. The mean ratio of cholesterol to triglycerides within VLDL was  $0.52 \pm 0.17$ , with the mean ratio of VLDL cholesterol to plasma triglycerides being  $0.33 \pm 0.09$ . In 57 patients (54%) both ratios were diagnostically elevated, 27 patients (26%) had a diagnostic ratio within VLDL only, while in 10 patients (10%) only the ratio related to plasma triglycerides was positive. We diagnosed dysbetalipoproteinaemia in 10 patients (10%) with a

mixed hyperlipidaemia who had non-diagnostic ultracentrifugation but an appropriate genotype.

ApoE genotyping data are available on all 105 patients. Fifty patients (48%) are homozygous for  $\epsilon 2$ , while 22 (21%) have ApoE2 (Arg145→Cys). This mutation causes dysbetalipoproteinaemia in an autosomal-dominant fashion with incomplete penetrance.<sup>22</sup> One patient (1%) has apoE2 (Lys146→Gln). In 32 patients (30%) we diagnosed dysbetalipoproteinaemia on phenotypic grounds, but have not as yet defined the underlying abnormality in apoE.

In 84 patients we had sufficient follow-up data to analyse response to treatment. We calculated response to therapy by comparing the best lipid values obtained during follow-up with the patient's lipid values in the untreated state. A mean reduction in total cholesterol of  $6.2 \pm 5.5$  mmol/l (52%) and in plasma triglycerides of  $5.5 \pm 8.6$  mmol/l (66%) was obtained. The best on-treatment lipid values were a cholesterol of  $5.7 \pm 2.4$  mmol/l, with plasma triglycerides of  $2.7 \pm 1.9$  mmol/l. All patients were given appropriate dietary advice and encouraged to exercise regularly. Conditions precipitating hyperlipidaemia such as hypothyroidism and diabetes were treated aggressively before lipid-lowering drug therapy was initiated. Five patients (6%) required no other therapy to control their lipids. Two (2%) were controlled on therapy with niacin alone, while 40 (48%) were treated with a fibrate. Nine patients (11%) were treated with a statin drug only, while 26



(31%) received a combination of a fibrate and statin. Two patients (2%) were treated with a combination of a fibrate and niacin.

## DISCUSSION

Our series of dysbetalipoproteinaemic patients is one of the largest reported from a single institution. Patients were selected using stringent phenotypic criteria in combination with genotypic information. A direct comparison of our experience with that previously reported<sup>13,23-26</sup> is not always possible, as the standards used to diagnose dysbetalipoproteinaemia over the years have shifted from a purely clinical diagnosis<sup>25</sup> to a more laboratory-based diagnosis.

As women in general only present after menopause, they are on average about 10 years older than men at presentation.<sup>3,24,25</sup> We also noted significantly earlier presentations in men than in women, but compared with another large series,<sup>24</sup> the difference was less impressive. Although our patients were generally older at presentation (48.8 years v. 43.8 years<sup>24</sup>), the reduced age gap between the sexes is mainly accounted for by older age at presentation in men locally (39.8 years v. 46.3 years<sup>24</sup>). The older age of presentation we report is probably due to the higher proportion of patients seen for secondary prevention. Furthermore, in a few cases there were substantial delays between the discovery of hyperlipidaemia and the referral of patients.

Untreated lipid values previously reported are similar to those we observed. Morganroth *et al.*<sup>24</sup> reported a mean total cholesterol of 11.7 mmol/l with plasma triglycerides of 7.9 mmol/l. In a pooled series of 185 patients<sup>3</sup> the mean reported total cholesterol was 11.7 mmol/l with plasma triglycerides of 6.4 mmol/l.

The frequency of clinical stigmata of lipid disorders is very variable, reflecting varying referral practices and diagnostic criteria. Some earlier series<sup>25</sup> included only patients with xanthomas. The reported incidence of palmar crease xanthomas ranges from 23% to 72%. However, in all series palmar and cutaneous xanthomas occur with approximately equal frequencies, with tendon xanthomas being the least common clinical manifestation of dysbetalipoproteinaemia.

Dysbetalipoproteinaemia is a highly atherogenic condition. As dysbetalipoproteinaemic patients usually only become hyperlipidaemic in adulthood, the exposure interval from hyperlipidaemia to the onset of atherosclerotic complications may be as short as a decade only. This is in marked contrast to patients with familial hypercholesterolaemia, who are hyperlipidaemic from birth and where untreated males on average have a first myocardial infarction at 43 years of age.<sup>27</sup> In our experience dysbetalipoproteinaemic patients also face the added risk of hypertriglyceridaemic pancreatitis. Peripheral vascular disease is believed to be more prevalent in this

condition than in other dyslipidaemias. In our experience the high frequency of peripheral vascular disease among females is of interest as it has not been described previously, although most case series did not differentiate clinical manifestations according to sex. Peripheral vascular disease and diabetes were strongly associated in both sexes.

Homozygosity for the  $\epsilon 2$  allele is the molecular defect in most patients<sup>3</sup> but in our series the apoE2 (Arg 145→Cys) mutation accounts for 21% of all cases in contrast to its very rare occurrence in other lipid clinics. The apoE2 (Arg145→Cys) mutation is particularly prominent in the black patients at our clinic. Similar regional clusterings of mutations causing dysbetalipoproteinaemia, possibly secondary to founder effects, have also been described in Spain<sup>28</sup> and in the Netherlands.<sup>29</sup>

Marked responsiveness to dietary and drug therapy is characteristic of dysbetalipoproteinaemia<sup>3,23,30</sup> and excellent control of hyperlipidaemia was achieved in nearly all our patients. Fibrates are the initial drug of choice as they are generally very effective and also have a cost advantage over statins in the public health sector.

We suspect that the diagnosis of dysbetalipoproteinaemia is frequently overlooked, especially in blacks who may have an additional burden of apoE2 (Arg145→Cys) to the generally accepted prevalence of 1 - 2% for apoE2/E2. Making the correct diagnosis will allow patients to receive appropriate therapy that will result in marked improvement in their prognosis. The children of parents with the apoE2(Arg145→Cys) mutation have a 50% chance of inheriting the mutation and regular lipid screening is advised for carriers of the gene.

Patients with severe hypercholesterolaemia require assessment of a fasting lipid profile<sup>2</sup> to distinguish between isolated hypercholesterolaemia and mixed hyperlipidaemia. We recommend that all patients with severe mixed hyperlipidaemia, or clinical signs such as palmar crease xanthomas and cutaneous or tendon xanthomas, or strong family histories of premature vascular disease, be referred to a lipid clinic to establish a diagnosis. Apart from benefiting patients there is also considerable scientific interest in further studying this condition in South Africa. Further studies are also required to determine the true frequency of the apoE2 (Arg145→Cys) mutation in the various population groups.

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## INTRAPARTUM-RELATED BIRTH ASPHYXIA IN SOUTH AFRICA — LESSONS FROM THE FIRST NATIONAL PERINATAL CARE SURVEY

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**Background.** The recent amalgamation of data by users of the Perinatal Problem Identification Programme (PPIP) throughout South Africa has culminated in the publication of the Saving Babies report.

**Objectives.** To determine the absolute rate of death from intrapartum-related birth asphyxia, and the contribution of intrapartum-related asphyxia to total perinatal mortality in South African hospitals, and to identify the primary obstetric causes and avoidable factors for these deaths.

**Methods.** The amalgamated PPIP data for the year 2000 were obtained from 27 state hospitals (6 metropolitan, 12 town and 9 rural) in South Africa. In PPIP-based audit, all perinatal deaths are assigned primary obstetric causes and avoidable factors, and these elements were obtained for all deaths resulting from intrapartum-related birth asphyxia.

**Results.** There were 123 508 births in the hospitals surveyed, with 4 142 perinatal deaths among infants  $\geq 1$  000 g, giving a perinatal mortality rate of 33.5/1 000 births. The perinatal mortality rate from intrapartum-related birth asphyxia was 4.8/1 000 births. The most frequent avoidable factors were delay by mothers in seeking attention during labour (36.6%), signs of fetal distress interpreted incorrectly (24.9%), inadequate fetal monitoring (18.0%) and no response to poor progress in labour (7.0%). The perinatal mortality rates for metropolitan, town and rural areas were 30.0, 39.4 and 30.9/1 000 births respectively. The contribution of intrapartum-related birth asphyxia to perinatal mortality in these areas was 10.8%, 16.7% and 26.4% respectively.

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