THE PLACENTA – A CINDERELLA STORY

INAUGURAL ADDRESS: PROF COLLEEN WRIGHT SEPT 2006

UNIVERSITEIT • STELLENBOSCH • UNIVERSITY

THE PLACENTA –
A CINDERELLA STORY

Colleen Wright

September 2006

The placenta – a Cinderella story

Inaugural lecture delivered on 19 September 2006
Prof CA Wright
Division of Anatomical Pathology
Faculty of Health Sciences, Stellenbosch University

Editor:	Mattie van der Merwe
Language editing:	Dr Edwin Hees
Design:	Heloïse Davis
Photograph of author:	Jacques Botha, www.jbphoto.co.za
Printing:	Africa Digital Printing Services

ISBN: 0-7972-1133-0

ABOUT THE AUTHOR

Colleen Anne Wright was born and matriculated in Cape Town, where she studied as a medical technologist in Microbiology, working at Conradie Hospital, the State Health Laboratories in Orange Street and the MRC.

She moved to Johannesburg to study medicine at the University of the Witwatersrand in 1981. Her son Ariel was born in 1982 and she was among the first Wits medical students to complete medicine with a child, setting many precedents for students who followed, such as taking him with her on her Rural Medicine modules. Her class was the last class taught by Professor Philip Tobias as Head of Anatomy and to have the privilege of being guided around Sterkfontein caves by this inspiring teacher.

After completing her internship at Baragwanath Hospital, Soweto, in 1988, she continued with her postgraduate training in Anatomical Pathology at Wits and the SAIMR, obtaining her FCPath (Anat Path), MRCPath (Histology), MMED (Anat Path) (Witwatersrand) and FIAC.

Professor Wright's main interest was perinatal pathology, a field which she developed and ran at Wits from 1990. In 1995 internationally respected cytopathology expert, Professor Gladwyn Leiman, asked her to become Head of the Cytopathology Unit. During her tenure Professor Wright became a strong advocate of fine needle aspiration biopsy in children as a means of expediting the diagnosis of tumours and infectious diseases, such as TB.

She returned to her beloved Cape Town in 2000, joining the Division of Anatomical Pathology at Stellenbosch University when her husband became Research Director at the UCT Graduate School of Business. She was elected Chair in 2002. Professor Wright's efforts to strengthen the Division have had two main focal areas: first, to make the Cytopathology Unit a leader in innovative diagnostic procedures and techniques; second, to develop Africa's first web-based Master's Degree in Cytopathology. In its second year, the new degree has already attracted students from throughout SA and other African countries.

Professor Wright has been an enthusiastic promoter of placental pathology and is involved in a number of projects, including the PASS Research Network, a Harvard-based research project on alcohol consumption in pregnancy and its links to stillbirth and SIDS. Her contribution to PASS was recognised recently in an appointment as Affiliate Professor of Pathology at the Children's Hospital Boston and the Harvard Medical School. She plans to establish the first perinatal pathology unit in South Africa within the Division in 2008.

ACKNOWLEDGEMENTS

> *This mortal world is fickle and unstable like unto a shifting shadow and the human life is like unto a mirage and a reflection on the water.*
>
> (Abdu'l-Baha)

Our lives, and what we achieve, are but a reflection of the lives around us.

And so I would like to thank

My colleagues and friends in the Faculty of Health Sciences, who have taken me into their hearts

Gael, a sister in a million, who has always been there for me

My precious children

Ariel, my son, who has survived a lifetime of a mother as a student and of whom I am so proud

Thandiwe, my daughter, beloved child of the light, who brings such joy into my life

and

Steve, my husband, partner and friend, you will always be the centre of my world

THE PLACENTA – A CINDERELLA STORY

INTRODUCTION

The placenta is the most under-examined, under-utilised and under-appreciated organ in the human body. The fetus is dependent on it for growth and survival. It provides oxygen and nourishment to the fetus by diffusion of soluble substances from the maternal blood in the intervillous space and the fetal blood in the fetal vessels within the villi. It also supplies an endocrine and excretory function. For 9 months it works day and night, devoting its entire life span to the fetus, and yet after delivery, with perhaps a cursory glance, it is relegated to the ashes…

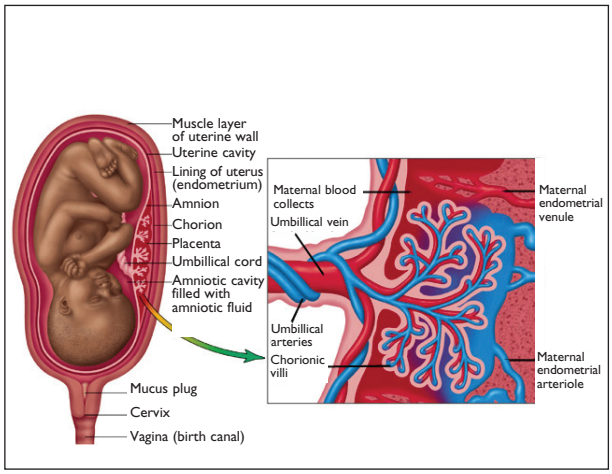

Figure 1:
The feto-placental unit

WHY IS THE PLACENTA IGNORED?

Most surgical pathologists do not want to examine placentas. They have limited exposure to placental pathology during their training and find it hard to become accustomed to the very different terminology applicable to this organ's pathology. The interpretation of the pathological features is difficult as there is no one-to-one correlation between the pathology, the clinical presentation or the outcome. This is reflected in the poor intra- and inter-observer correlation obtained in the few studies which have been conducted in this area (Naeye 1991; Badawi et al. 2000). The outcome is that the placenta is globally acknowledged in general pathology as being "not examinable", which perpetuates this gap in the knowledge of general pathologists. The placenta is therefore usually relegated to specialist perinatal pathologists or pathologists with a special interest in placentas, but in countries such as the UK perinatal pathology has a low status (*Fetal and perinatal pathology* 2001). An additional factor which makes pathologists reluctant to examine placentas is their sheer number. However, if good guidelines are established as to which placentas are submitted for pathological examination, pathologists would not feel overwhelmed.

WHY SHOULD THE PLACENTA BE EXAMINED BY A PATHOLOGIST?

Globally there are 4 million neonatal deaths annually. Approximately 99% of these occur in low- and middle-income countries. The highest rates are in sub-Saharan Africa, and 23% are estimated to be related to intrapartum events (Lawn et al. 2005a).

In addition 4 million stillbirths occur annually and 26% of these are thought to occur during labour (intrapartum deaths).

These figures are, however, estimates as only 3% of neonatal deaths and stillbirths occur in countries with verifiable data.

In South Africa, there are limited data available, and this shows that the contribution of intrapartum asphyxia to perinatal mortality varies from 10.8% in metropolitan areas to 26.4% in rural areas.

In South Africa data are collected in many obstetric units in state hospitals in urban and rural areas, and amalgamated in the Perinatal Problem Identification Programme (PPIP) to provide information on the causes of perinatal death, as well as on contributing or avoidable factors. This not only quantifies the problem, but provides information which may highlight areas of substandard care and may guide health care policy.

The PPIP data analysed from 2000-2002 reflected that the commonest cause of primary obstetric death was recorded as UNKNOWN (Pattinson 2003).

CONTRIBUTION OF PLACENTAL PATHOLOGY

Examination of the placenta by a pathologist can provide valuable information which may not be determined clinically. There may be poor correlation between maternal indicators of infection and placental findings, and placental causes of fetal and perinatal death may be clinically silent, e.g. placental maturation defect and fetal thrombotic vasculopathy (Stallmach 2004). Clinical entities such as intrauterine growth retardation (IUGR) have a multifactorial aetiology related to fetal, maternal and placental pathology.

Through histopathological examination of the placenta the pathophysiology of an adverse pregnancy outcome may be explained, and this may contribute to the management of subsequent pregnancies, as many of the maternal and placental causes of this tragedy may recur. Identification of specific pathology in the placenta such as chorioamnionitis or villitis due to Cytomegalovirus infection may assist in the management of the neonate, both in the acute and longer term.

Placental examination is vital in the determination of timing of events that led to adverse pregnancy outcome and in doing so may assist in the medico-legal assessment of cases.

These contentions are validated by a few specific cases received in our laboratory.

CASE 1

A 24-year-old primigravida booked early and was followed through an uneventful pregnancy. At 37 weeks she reported absence of fetal movements for 1 day. On examination an intrauterine death was diagnosed, labour induced and she delivered a normal, fresh stillbirth baby.

The placenta was noted to be pale.

Diagnosis: Sudden unexpected intrauterine death, cause unknown

Placental pathology: Maturation defect

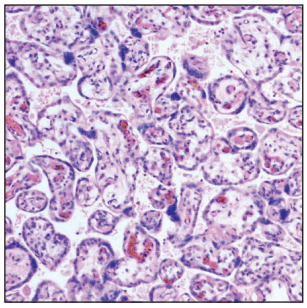

Figure 2a:
Maturation defect

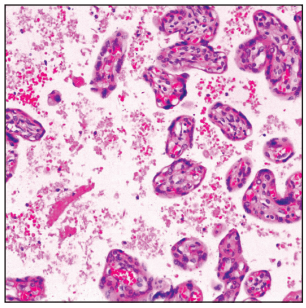

Figure 2b:
Normal-term placenta

Maturation defect/arrest

Approximately 3-4 / 1000 uneventful viable pregnancies will end in sudden in utero death. This accounts for 50% of all cases of perinatal mortality in developed countries. The commonest cause is placental maturation defect or maturation arrest. The incidence of this entity has been reported as 5.7% and is associated with fetal death in 2.3% cases. Of even greater significance to the clinician is that the recurrence risk is 5.4% or a 10-fold increase (Stallmach 2002; 2004).

Histopathology shows markedly reduced vascularity of terminal villi with a paucity of vasculosyncytial membranes. This would result in poor transfer of oxygen to the baby and resultant hypoxia.

CASE 2

A 32-year-old female, with a history of a previous intrauterine death, booked late for antenatal care. At 36 weeks she noticed decreased fetal movements and on examination an intrauterine death was diagnosed.

She delivered a fresh stillbirth, and the baby was noted to show intrauterine growth retardation.

Diagnosis: Placental insufficiency

Placental pathology: Fetal thrombotic vasculopathy

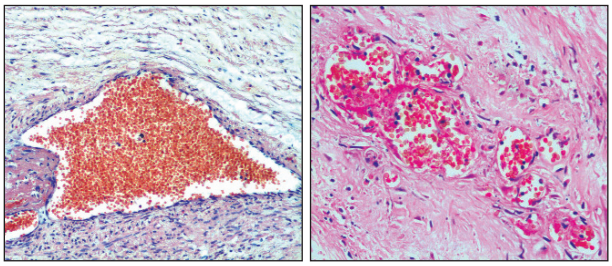

Figure 3:
Organising thrombi in chorionic vessels

Fetal thrombotic vasculopathy

Demonstration of thrombi in the placental vessels is evidence that thrombi have occurred in the fetal circulation prior to delivery. This may result in pre- or perinatal death, neonatal encephalopathy and cerebral palsy. The pathogenesis may be due to emboli, thrombi elsewhere in the fetoplacental circulation or hypoxia secondary to extensive placental damage (Kraus & Acheen 1999; McDonald et al. 2004).

Histopathology shows extensive avascular villi, because of thrombosis of fetal vessels, which may be seen as obliterated stem arteries, occlusive thrombi, recent or undergoing organisation and hemorrhagic endovasculitis.

CASE 3

A 22-year-old female presented in preterm labour. At delivery the placenta was noted to show 15% retroplacental haemorrhage. The baby had poor Apgars at birth.

Diagnosis: Preterm labour because of abruptio placenta

Placental pathology: Chorioamnionitis due to Candida infection

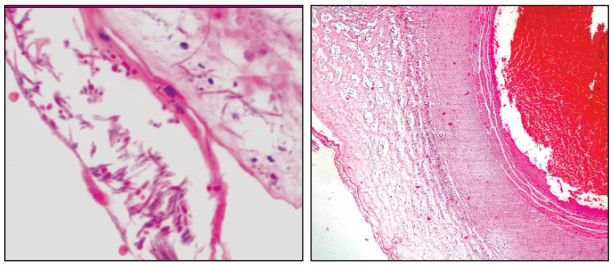

Figure 4:
Funisitis (inflammation of the umbilical cord) due to Candida infection

Ascending infection – chorioamnionitis

Contrary to prior belief, this has been shown to be a cause of premature rupture of membranes and not a consequence and may be associated with abruptio placenta. Although the fetus may present with aspiration pneumonia and sepsis, damage may also result as a consequence of cytokine mediated vasoconstriction of the fetal vessels resulting in fetal asphyxia, leukomalacia and death. In addition, as the infection causes initiation of premature labour the fetus, though not infected, may be severely compromised as a result of the complications associated with prematurity.

The fetal vascular response – intensity and distribution – usually correlates with neonatal sepsis or neurologic impairment.

LITIGATION

In a survey of obstetricians conducted in 1985 and 1987 among members of the American College of Obstetricians and Gynecologists (ACOG) it was noted that 70% of obstetricians were sued at least once and 20% of all these lawsuits were related to brain-damaged infants. In a later survey of the ACOG in 1992, the number of obstetricians sued at least once had risen to 79%, with 33% lawsuits related to brain-damaged infants and 13% to stillbirth/neonatal deaths (Roberts 1993).

A 1985 NIH report stated that in the USA there were 850,000 mentally retarded children, 750,000 young people with cerebral palsy, and 10% of all school-age children were disabled. It was estimated that 42 million Americans have some form of neurologic or communicative disorder (Roberts 1993).

This has spawned a global childbirth litigation industry. The problem is not confined to the USA – in 2001 the British NHS faced a 4.2 billion dollar medical negligence bill (Hankins et al. 2003b).

Cerebral Palsy

Cerebral palsy (CP) was until fairly recently attributed to intrapartum hypoxia, and the obstetricians and delivery units bore the brunt of the anger and disappointment of the parents. The prevalence of CP remains constant at 1.5 to 2.5/1000 deliveries (1970-2000), unchanged despite significant improvement in fetal monitoring and neonatal intensive-care practice (Hankins et al. 2003b). There has been a minimal reduction in term Hypoxic Ischaemic (HI) injury, but this has been offset by the increasing number of very-low-birthweight survivors as a consequence of this increased monitoring and sophisticated care (Kraus 2003). Caesarean section rates have also increased by a factor of 10 as a result of this increase in fetal monitoring. The irony is that studies have shown that most children with CP showed no evidence of "fetal distress" prior to delivery.

Neonatal encephalopathy

Neonatal encephalopathy (NE) occurs in 3.8/1000 term births but Hypoxic-Ischaemic Encephalopathy (HIE) in 1.9/1000 births. This indicated the pathway from intrapartum HI injury to CP must progress through neonatal encephalopathy (Hankins et al. 2003a).

There are four essential criteria to define whether an intrapartum event was sufficient to cause CP and all other identifiable etiologies must be excluded.

The Western Australia case-control study into CP showed that 69% of children with CP had only antepartum risk factors, 25% had ante- and intrapartum risk factors, 2% had no recognised risk factors and only 4% of children with CP had intrapartum risk factors only (Badawi et al. 1998).

Blair and Stanley (1988) showed subsequently that in only 8% of children with spastic CP was intrapartum hypoxia the possible cause of brain damage.

It is widely accepted now that multiple early and recent insults act together to increase the risk of brain injury at birth, i.e. perinatal asphyxia may be a CONSEQUENCE of rather than a CAUSE of neurological injury (Cox 2004).

In 2000 Redline investigated placental lesions associated with CP and NI at term in 40 infants with NI vs. 176 meconium-stained infants at low risk for NI. He documented the presence or absence of 5 lesions occurring within days of labour and delivery:

1. Meconium-associated vascular necrosis of the umbilical cord;
2. Severe fetal chorioamnionitis;
3. Chorionic vessel thrombi;

4. Increased nucleated red blood cells in the fetal vessels;
5. Retro placental haemorrhage (chronic).

He also documented 4 lesions known to have onset long before labour and delivery:

1. Diffuse chronic villitis;
2. Extensive avascular villi;
3. Diffuse chorionic haemosiderosis;
4. Perivillous fibrin.

In this study the risk of NI increased as a function of the number of lesions present (OR, 10.1: 95% CI, 5.1-20) as well as the temporal distribution of lesions (OR, 94.2; 95% CI, 11.9-747), showing that previous insults decrease the threshold for more recent events to cause severe injury to the fetus.

CASE 4

A 21-year-old primigravida was referred to Tygerberg with mid-pelvic arrest and meconium-stained liquor. In theatre delivery was attempted under spinal anaesthesia. The mother developed bradycardia, resuscitation was started and an emergency caesarian section performed.

The baby was delivered with signs of neonatal encephalopathy.

Diagnosis: Intrapartum hypoxia

Placental pathology: Meconium-associated vascular necrosis of the umbilical vessels

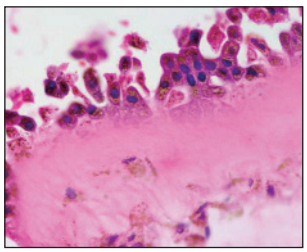

Figure 5a:
Meconium in amnion and meconium-laden macrophages in chorion

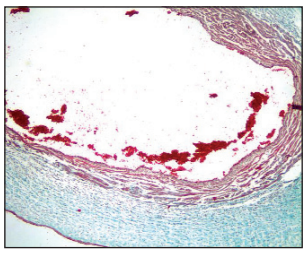

Figure 5b:
Destruction of media of umbilical vessel

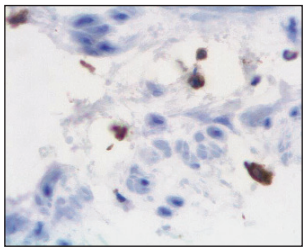

Figure 5c:
Macrophages labelled with CD 68 in umbilical vessels

Meconium

Meconium may normally be passed by term fetuses during labour. If occurring in preterm fetuses or if present prior to labour, it may be considered a possible indication of fetal distress. Histopathology may estimate the duration of meconium passage. Macrophages containing meconium are present at the chorionic surface within 2-3 hrs and deep in membranes at 6-12 hrs.

Meconium in the amniotic fluid may cause vasoconstriction of umbilical blood vessels and hypoperfusion of the fetus if exposure is prolonged. Macrophages and necrotic arterial media in the umbilical cord indicate exposure 48 hrs prior to delivery, and this meconium-associated vascular necrosis of the umbilical cord shows significant correlation with severe neonatal encephalopathy and cerebral palsy (Redline et al. 2000).

PLACENTAL PATHOLOGY IN TYGERBERG HOSPITAL

Placentas from the obstetric unit are submitted for histopathology according to defined criteria which were established by obstetricians, neonatologists and pathologists. An audit of the value of the placental histology was conducted on all placentas submitted from Tygerberg Hospital obstetric unit for a 25-month period during 2004-2006. A total of 848 placentas were received, accounting for 15% of all deliveries (Munbodh et al. 2006).

We looked at the correlation between the proposed clinical diagnoses and the corresponding histopathological diagnoses.

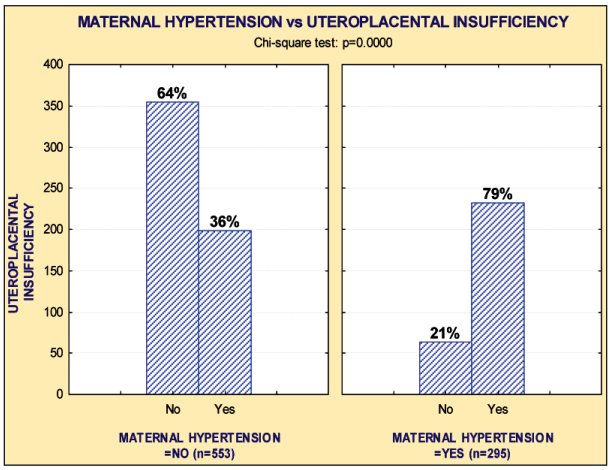

Figure 6:
Maternal hypertension vs. uteroplacental insufficiency

Maternal hypertensive disorders are common in this population and may result in maternal under-perfusion of the placenta, resulting in a placenta unable to support the needs of the fetus. In this study, however, 36% of patients with no clinical evidence of hypertension showed features of uteroplacental insufficiency, reflecting the multifactorial aetiopathogenesis of this pathological entity.

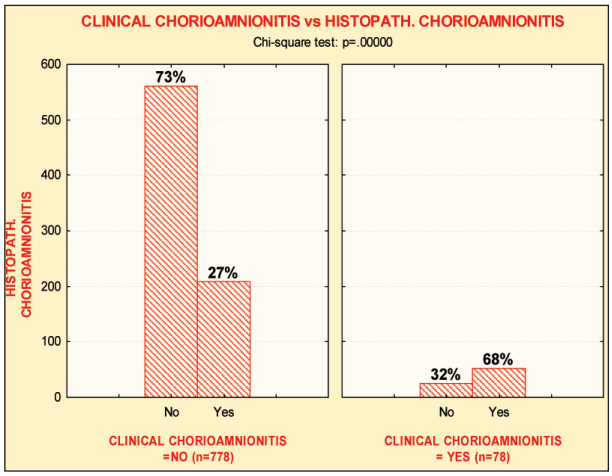

Figure 7:
Clinical vs. histopathological chorioamnionitis

There was reasonable correlation between clinically suspected chorioamnionitis and histopathological confirmation of inflammation, but the severity of the maternal and/or fetal presentation did not always correlate with the placental grade of inflammation. This can partly be explained by the virulence of the organisms responsible. Of concern is the number of placentas showing acute chorioamnionitis which was clinically silent.

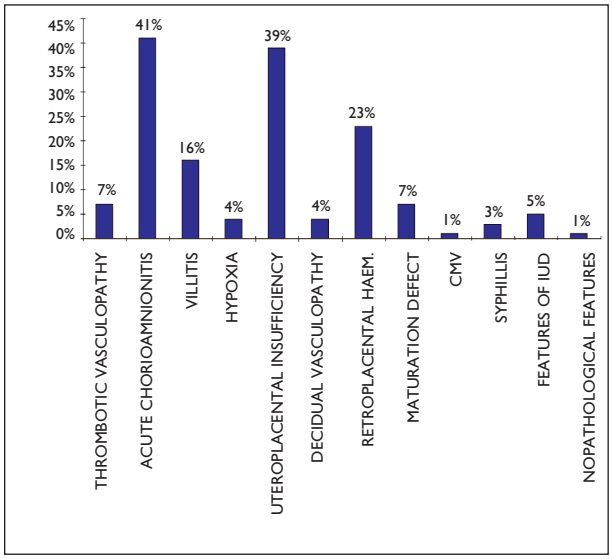

Figure 8:
IUD – cause unknown (160 cases)

In cases associated with adverse pregnancy outcome, for which the cause was clinically unknown, the spectrum of histopathological diagnoses was described.

Acute chorioamnionitis and uteroplacental insufficiency accounted for the majority of these diagnoses and were sometimes co-existent. Although some of these patients were unbooked, many were receiving antenatal care, but these entities were clinically silent.

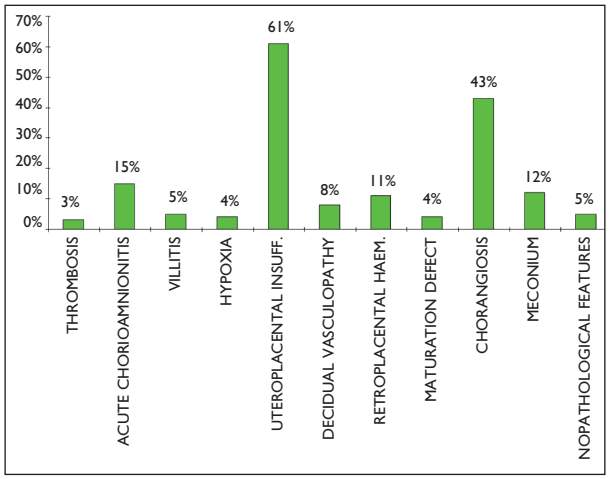

Figure 9:
Fetal distress (211 cases)

A very high percentage of placentas from fetuses presenting with fetal distress severe enough to warrant delivery showed histopathological features of uteroplacental insufficiency. The placental function has been compromised to the degree that it can no longer support the needs of the growing fetus and unless the fetus is delivered either spontaneously or electively, death will be the outcome.

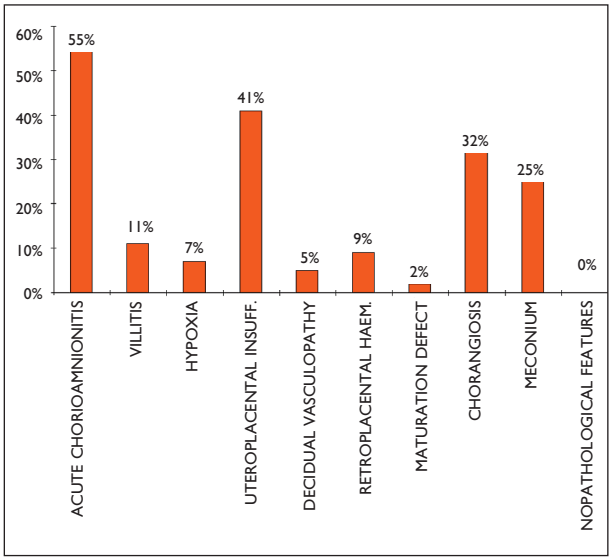

Figure 10:
Preterm labour (44 cases)

Acute chorioamnionitis was seen in just over half of these placentas, and overlapped with premature rupture of membranes. This finding reiterated the need for careful assessment of patients prior to suppressing labour.

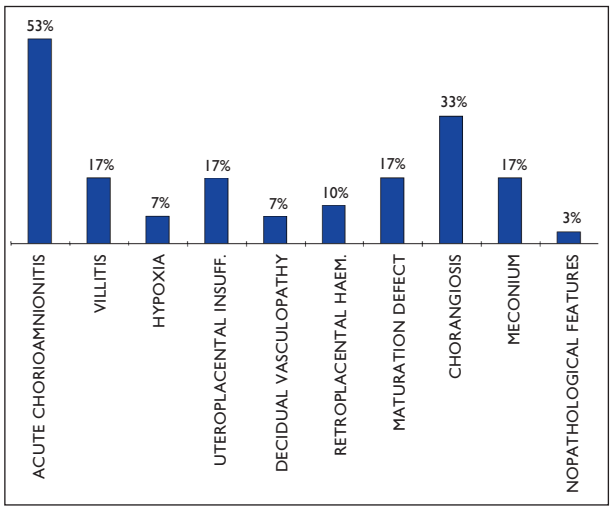

Figure 11:
Suspected intrapartum hypoxia/death (30 cases)

This represents a very important group of placentas. In all of these the clinical diagnosis was suspected intrapartum hypoxia or death. However, intrauterine infection was present in 70% of these placentas, confirming the fetus entered labour in an already compromised state. Without the pathology of the placenta, the medico-legal liability in more than 90% of these cases may well be placed at the door of the obstetrician and delivery unit.

CONCLUSION

At last, after decades of being ignored, the placenta has come of age. Her beauty and the valuable contribution she can make to understanding adverse pregnancy outcome are being acknowledged by pathologists, neonatologists, obstetricians and administrators of health care institutions and medical insurance companies. Cinderella is going to the ball!

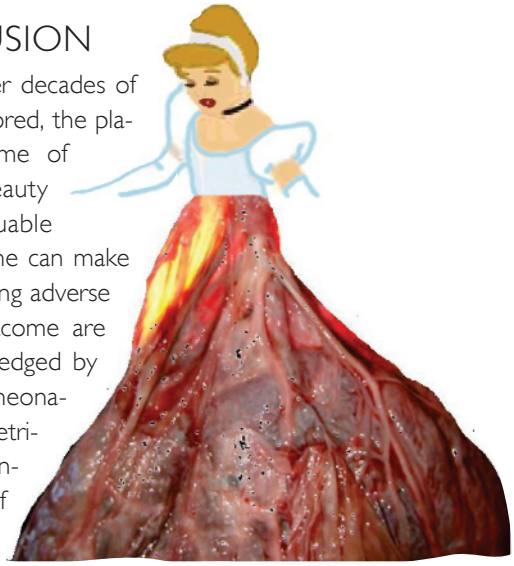

Figure 12:
Cinderella is going to the ball

REFERENCES

Altshuler G, Hyde SR 1996. Clinicopathological implications of placental pathology [The Placenta in Clinical Practice]. *Clin Obstet and Gynecol* 39(3):549-570

Badawi N, Kurinczuk JJ, Keogh JM, Chambers HM, Stanley FJ 2000. Why is the placenta being ignored? *Aust N Z Obstet Gynaecol* 40(3):343-6

Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ 1998. Intrapartum risk factors for newborn encephalopathy: the Western Australian case control study. *BMJ* 317(7172):1554-8

Benirschke K 1990. The placenta in the litigation process. *Am J Obstet Gynecol* 162(6):1445-50

Blair E, Stanley FJ 1988. Intrapartum asphyxia; a rare cause of cerebral palsy. *J Pediatr* 112:515-519

Buchmann EJ, Pattinson RC, Nyathikazi N 2002. Intrapartum-related birth asphyxia in South Africa – lessons from the first national perinatal care survey. *SAMJ* 92(11):879-901

Byer CO, Shainberg LW, Galliano G 1999. *Dimensions of Human Sexuality*. New York, McGraw-Hill

Stillbirth, neonatal and post-neonatal mortality 2000-2003, England, Wales and Northern Ireland. Confidential enquiry into maternal and child health 2005. London: RCOG Press

Cox P 2004. *Perinatal brain injury.* Paediatric Pathology Society Update Course, Western Cape

Fetal and perinatal pathology. Report of a joint working party 2001. London: RCOG Press

Hankins G, Erickson K, Zinburg S, Schulkin J 2003a. Neonatal encephalopathy and cerebral palsy: A knowledge survey of fellows of the American College of Obstetricians and Gynecologists. *Obstet Gynecol* 10(1):11-7

Hankins G, Speer M 2003b. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstet Gynecol* 102(3):628-36

Khong TY 1997. From delivery suite to laboratory: optimising returns from placental examination in medico-legal defense. *Aust N Z Obstet Gynaecol* 37(1):1-5

Kraus FT 2003. Perinatal pathology, the placenta and litigation. *Hum Pathol* 34(6):517-21

Kraus FT, Acheen V 1999. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. *Hum Pathol* 30(7):759-69

Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team 2005a. 4 million neonatal deaths: When? Where? Why? *Lancet* 356(9462):891-900

Lawn JE , Shibuya K, Stein C 2005b. No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. *Bull World Health Organ* 83(6):409-17

McDonald D, Kelehan P, McMenahim J, Gorman W, Madden D, Tobbia I, Mooney E 2004. Placental Fetal Thrombotic Vasculopathy is associated with neonatal encephalopathy. *Hum Pathol* 35:875-80

Munbodh R, Hall D, Steyn W, Wright C 2006. Pathology examination of placentas in a high-risk population group: Comparison of the clinical and histopathological diagnoses. *Proceedings of IAP Congress*. Durban

Naeye R, Travers H 1991. CAP Conference XIX on the examination of the placenta: Report of the working group on the role of the pathologist in malpractice litigation involving the placenta. *Arch Pathol Lab Med* 115(7):717-19

Pattinson RC 2003. Why babies die – a perinatal care survey of South Africa, 2000-2002. *SAMJ* 93(6):445-450

Redline R, Wilson-Costello D, Borawski E, Fanaroff A, Hack M 2000. The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. *Pediatr Res* 47(6):721-6

Redline R, O'Riordan MA 2000. Placental lesions associated with cerebral palsy and NI following term birth. *Arch Pathol Lab Med* (124):1785-91

Rhone J 2003. The association of placental abnormalities with maternal and neonatal clinical findings: a retrospective study. *Obstet Gynaecol Can* 25(2):123-8

Roberts DK 1993. A Guest Editorial: Medico-legal aspects of placental examination. *Obstet Gynecol Surv* 48(12):777-8

Stallmach T 2004. *Fetal and perinatal death-specific and unknown causes.* Paediatric Pathology Society Update Course , Western Cape

Stallmach T 2002. The clinical relevance of examination of the placenta: Rescue by birth: defective placental maturation and late fetal mortality. *Proceedings of the XXIVth International Congress of the IAP*. The Netherlands