# Mid-pregnancy genetic terminations of pregnancy — postnatal assessment and management

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*Study objective.* To assess the need for and ability to apply a postnatal assessment protocol (PNAP), consisting of clinical examination, photographs, radiographs, chromosomal analysis and postmortems, of fetuses from mid-pregnancy genetic terminations of pregnancy.

*Design.* Prospective hospital-based study.

*Setting.* The maternity unit at the Pretoria Academic Hospital.

*Main results.* Fifty consecutively delivered fetuses were assessed by means of the PNAP after genetic termination of pregnancy. A definitive prenatal diagnosis was available in 17 (34%) cases. In 33 (66%) cases the termination was undertaken on the basis of a provisional prenatal diagnosis which was confirmed postnatally in 12 (24%) cases; a definitive postnatal diagnosis could not be confirmed in 5 (10%) cases. In the remaining 16 (32%) cases a totally different postnatal diagnosis was obtained. The definitive postnatal diagnoses in the 28 cases with provisional prenatal diagnoses were confirmed by clinical examination in 13 (26%), by chromosomal analysis in 7 (14%), by postmortem in 5 (10%) and with radiographs in 3 (6%). On retrospective analysis, 22 of the 33 provisional prenatal diagnoses could have been confirmed using available radiographs, chromosome results and photographs only.

*Conclusions.* Genetic terminations of pregnancy are a subgroup of stillbirths for which a PNAP is essential to ensure that appropriate postnatal genetic counselling can be given to the parent(s).

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The postnatal investigation of stillbirths and neonatal deaths, using a protocol of clinical examination, photographs, radiographs, chromosomal analysis and postmortem examination of the fetus/newborn (PNAP), is well established.[1,2] This protocol is utilised to obtain epidemiological information related to stillbirths and neonatal deaths, but is also of clinical relevance in obtaining a specific diagnosis to ensure that appropriate postnatal counselling can be offered to the parent(s). In cases of congenital anomalies, appropriate postnatal genetic counselling is essential as there is a risk of recurrence of the condition in a future pregnancy, and parents need to be able to make informed decisions about future pregnancies.[1,2]

Section 3(1)(c) of the Abortion and Sterilisation Act 2 of 1975[3] states that a legal termination of pregnancy (TOP) may be undertaken where there is a serious risk that the child will suffer from a physical or mental defect of such a nature that he/she will be irreparably handicapped.

By definition, second- and third-trimester fetuses from TOPs undertaken for genetic reasons, as stipulated by the Act, will be at high risk of congenital anomalies. They therefore represent a subgroup of stillborn infants in whom the application of a PNAP should be a *sine qua non*.

We present the results of a prospective study, applying a postnatal management protocol to 50 consecutive fetuses of second- and third-trimester genetic TOPs. The aim of this study was to assess the need for the application and ability to apply a PNAP to this subgroup of stillbirths, with particular reference to the circumstances that apply in hospitals in South Africa, and to assess how such a protocol could be adapted to these circumstances.

## Subjects and methods

This study was undertaken at the Pretoria Academic Hospital's maternity unit between 1 January 1993 and 31 October 1994, and included 50 fetuses delivered consecutively in terms of Section 3(1)(c) of the Abortion and Sterilisation Act 2 of 1975.[3] The fetuses were examined by a clinical geneticist (A.L.C.), or a genetically trained nursing associate (H.J.S.v.d.B. and P.v.R.) when A.L.C. was not available. The clinical features were documented and radiographs of the whole fetus taken. Specimens of fetal skin and, if possible, fetal blood were obtained for chromosomal analysis. Photographs were taken of the whole fetus (and specific parts thereof when these were considered necessary to document specific clinical features). Finally, if the prenatal history and investigation, and postnatal clinical examination and radiographs did not suggest a specific diagnosis, a fetal postmortem was undertaken.

Where possible, a definitive diagnosis was made on the basis of the above protocol, and the parent(s) of the affected fetus were offered postnatal genetic counselling.

## Results

Fifty fetuses were examined, 33 (66%) by a clinical geneticist and 17 (34%) by a trained genetic nursing associate. Radiographs were obtained in 44 (88%) cases. Chromosome analysis of fetal skin and/or blood was undertaken on 46 (92%) fetuses, and a successful result was obtained in 35 (70%). Clinical photographs were available in 35 (70%) cases and 5 (10%) postmortems were performed. The information obtained was analysed, and produced the following results.

Prior to TOP, a confirmed definitive diagnosis was available in 17 (34%) fetuses, the remaining 33 (66%) having prenatal provisional diagnoses that required postnatal confirmation. In 12 (24%) cases this prenatal provisional diagnosis was confirmed, and in 16 (32%) cases the prenatal diagnosis was completely altered postnatally (Table I). In 5 (10%) cases, a definitive postnatal diagnosis could not be reached, as postnatal chromosome cultures failed to show growth. The diagnoses are listed in Table I: 12 (24%) cases had an idiopathic aetiology, 12 (24%) were considered to have multifactorial causation, 15 (30%) were chromosomal abnormalities, 6 (12%) were consequent on maternal teratogenesis and 5 (10%) were due to Mendelian inheritance.

The commonest reason for TOP was neural tube defects (NTDs). These included 7 (14%) anencephalics, 8 (16%) cases of spina bifida (5 with hydrocephalus), 2 (4%) encephaloceles and a meningocele, which was confirmed postnatally as a case of exstrophy of the cloaca sequence (Table I). Chromosomal abnormalities, including a trisomy 18, 2 chromosomal translocations and a patient with mosaicism, were found in 4 of the NTD group. The mother of 1 anencephalic was diagnosed postnatally as having phenylketonuria (PKU).

Excluding the 17 (34%) cases in which a definitive diagnosis was available prenatally, postnatal confirmation of a definitive diagnosis was obtained in 28 (56%) cases by clinical examination of the fetus in 13 (26%) cases, chromosomal analysis in 7 (14%) cases, postmortem in 5 (10%) cases and radiographs in 3 (7,5%) cases. In 5 (10%) cases a definitive postnatal diagnosis was not confirmed. When the 33 cases with a provisional prenatal diagnosis were analysed retrospectively, using available photographs, radiographs and chromosomal results in 22 (44%) cases, a definitive diagnosis could be made.

A definitive diagnosis, on the basis of which postnatal genetic counselling could be undertaken, could thus be made from the prenatal history and investigations, and postnatal radiographs, photographs and chromosomes in a total of 39 (78%) cases. The remaining 11 (22%) cases not diagnosable in this manner, included 5 (10%) cases that required a postmortem, a single case of X-linked hydrocephalus (diagnosed clinically postnatally), and 5 (10%) cases, including the anencephalic associated with maternal PKU, in which postnatal chromosomal culture was unsuccessful. A definitive diagnosis for postnatal genetic counselling was thus obtained in 45 cases (90%) in this study.

## Discussion

Currently, prenatal diagnostic technology is capable of diagnosis of nearly 400 different fetal conditions,[4] and the number continues to increase. The diagnosis of many of

**Table I. Pre- and postnatal diagnosis in 50 genetic TOPs**

| Prenatal diagnosis | No. | % | Postnatal diagnosis | No. | % | Diagnosis modified by PNAP |
|---|---|---|---|---|---|---|
| Neural tube defects (NTDs) | 18 | 36 | Isolated NTDs | 12 | 24 | No |
| | | | Chromosomal translocation | 2 | 4 | Yes |
| | | | Chromosomal mosaicism | 1 | 2 | Yes |
| | | | Trisomy 18 | 1 | 2 | Yes |
| | | | Exstrophy — cloaca sequence | 1 | 2 | Yes |
| | | | Anencephaly/maternal PKU | 1 | 2 | Yes |
| Structural brain defect | 2 | 4 | | | | |
| Hydrocephalus | 1 | 2 | X-linked hydrocephalus | 1 | 2 | Yes |
| Holoprosencephaly | 1 | 2 | Chromosomal translocation | 1 | 2 | Yes |
| Abdominal wall defect | 2 | 4 | | | | |
| Early urethral obstruction sequence | 1 | 2 | Early urethral obstruction sequence | 1 | 2 | No |
| Omphalocele | 1 | 2 | Omphalocele | 1 | 2 | No |
| Renal anomaly | 5 | 10 | | | | |
| Renal agenesis | 1 | 2 | Potter syndrome | 1 | 2 | No |
| Enlarged kidneys/hydrops/ oligohydramnios | 1 | 2 | Bilateral multicystic kidneys with Potter syndrome | 1 | 2 | Yes |
| Bilateral cystic kidneys | 1 | 2 | Bilateral multicystic kidneys | 1 | 2 | Yes |
| Infantile polycystic kidneys | 2 | 4 | Polycystic kidneys | 2 | 4 | No |
| Cardiac defect | 1 | 2 | | | | |
| Autosomal dominant congenital heart block | 1 | 2 | Congenital heartblock | 1 | 2 | No |
| Skeletal dysplasias | 3 | 6 | | | | |
| Short limbed dwarfing | 1 | 2 | Thanatophoric dysplasia | 2 | 4 | Yes |
| | | | Achondrogenesis (type 1B) | 1 | 2 | Yes |
| Maternal teratogenesis | 6 | 12 | | | | |
| HIV positivity | 1 | 2 | HIV positivity | 1 | 2 | No |
| Roaccutane | 3 | 6 | Roaccutane | 3 | 4 | No |
| Antimetabolites | 2 | 4 | Antimetabolites | 2 | 4 | No |
| Cystic hygroma | 3 | 6 | Cystic hygroma | 2 | 4 | No |
| | | | Turner syndrome | 1 | 2 | Yes |
| Chromosomal anomalies | 8 | 16 | | | | |
| Trisomy 21 | 5 | 10 | Trisomy 21 | 5 | 10 | No |
| Trisomy 18 | 2 | 4 | Trisomy 18 | 2 | 4 | No |
| Turner syndrome | 1 | 2 | Turner syndrome | 1 | 2 | No |
| Multiple congenital anomalies | 2 | 4 | Atypical acrofacial dysostosis[10] | 1 | 2 | Yes |
| | | | Trisomy 18 | 1 | 2 | Yes |

these conditions, using maternal ultrasound scanning, amniocentesis and cordocentesis, is only possible in the second and third trimesters.

Stillbirth is defined as fetal loss during the late second and third trimester of pregnancy.[1] In the circumstances prescribed by the Act,[3] the diagnosis or serious risk of a fetal congenital anomaly allows for a TOP to be offered to the parent(s). Second- and third-trimester genetic TOPs therefore constitute an important subgroup of stillbirths, which may not have occurred in the normal course of events. Approximately 25% of stillbirths are due to fetal congenital anomalies,[1,5] whereas we report 44 (88%) of the fetuses examined clinically as having congenital anomalies, the exceptions being 6 (12%) cases of maternal teratogenesis (Table I). Therefore, the likelihood of obtaining positive results with the PNAP is very high in this group of patients.

To ensure that a genetic TOP fell within the ambit of the law, a prenatal diagnosis of a significant congenital anomaly, or the risk thereof, was necessary. In all 50 patients a significant prenatal diagnosis was available (Table I), but in only 17 (34%) was there a definitive prenatal diagnosis which allowed absolute postnatal genetic counselling. Of the remaining 33 (66%) patients, the prenatal provisional diagnosis was confirmed in only 12 (24%). In 16 (32%) cases, the prenatal diagnoses were completely altered by the application of the PNAP. This is comparable to the figure of 40% documented by Clayton-Smith *et al.*,[6] if the differing methods of case ascertainment are taken into consideration.[6] The remaining 5 (10%) cases included 3 with NTDs and 2 with a cystic hygroma. Postnatal chromosomal cultures failed to show growth in these cases, and a definitive diagnosis could therefore not be made. Two of the NTDs were considered to be isolated in origin, and the aetiology in the third fetus was complicated by the mother's being diagnosed postnatally with PKU. Postnatally, the fetuses with the cystic hygromas were clinically diagnosed as having Turner syndrome.

It has been observed that counsellors who provide postnatal counselling to parents who have suffered a stillbirth frequently do so with only the inadequate information available to them from the fetal death report.[2] Given the information available from the prenatal diagnosis in genetic TOPs and the fetal death report, this information would still have been inadequate for appropriate postnatal genetic counselling in up to 66% of cases in this study. With the PNAP, the number of definitive postnatal diagnoses enabling appropriate genetic counselling was increased to 45 (90%). However, in the remaining 5 cases, the information that could be given to the parent(s) was germane for future reproductive decisions.

An idiopathic aetiology was recorded in 24 (48%) of the TOPs, including 12 (24%) fetuses with isolated NTDs.

Chromosomal abnormalities were the second commonest reason for TOP (30%). Trisomy 21 was present in 5 (10%) fetuses, in all of whom the diagnosis had been confirmed prenatally. Trisomy 18 occurred in 4 (8%) fetuses, in 2 of whom it was confirmed cytogenetically prior to TOP. The remaining chromosomal abnormalities were 2 Turner syndromes, 3 translocations and a mosaicism. Teratogenesis, including maternal HIV positivity, was the reason for 6 (12%) of the TOPs. The individual case of maternal HIV positivity was included in this category as the TOP was undertaken under section 3(1)(c) of the Act[3] and we consider maternal HIV positivity, by definition,[5] to be potentially teratogenic. Mendelian inheritance was the cause of the congenital anomalies in 5 (10%) of the fetuses: 3 of autosomal recessive inheritance and single cases each of autosomal dominant and X-linked recessive inheritance.

The commonest single reason for TOP was NTDs. Seven anencephalics, 8 meningomyeloceles (5 with hydrocephalus), 2 encephaloceles and a meningocele were diagnosed prenatally. However, postnatally, only 12 were considered to have isolated NTDs. Three of the meningomyeloceles were secondary to chromosomal abnormalities — 2 translocations, both of which were carried by a parent, and a trisomy 18. One encephalocele was a chromosomal mosaic, the meningocele was part of an exstrophy of the cloaca sequence, and 1 NTD case was the anencephalic whose mother was diagnosed postnatally as having PKU. Maternal PKU is associated with an increased incidence of stillbirths and serious damage to the fetus, including microcephaly and mental retardation, congenital heart defects and vertebral anomalies.[5,7] To our knowledge it has not previously been described in association with NTD, in particular anencephaly. If a PNAP had not been applied in these fetuses terminated for NTDs, 6 (30%) of the parents who underwent TOP for a NTD could have been given incorrect postnatal genetic counselling. This situation has been documented previously.[6]

Woods and Draper[8] noted that most major abnormalities in stillborn infants could be recognised if they were carefully examined. Considering the above findings on the NTD cases and previous experience with trisomy 18,[9] we would dispute this; to ensure adequate evaluation of genetic TOPs, a PNAP must be undertaken. We would, however, concur that a postmortem is not an absolute prerequisite in cases of TOP for genetic reasons and is necessary mainly in cases of cardiac and renal abnormalities (especially in those with no previous family history); we further feel that a postmortem should also be undertaken after clinical examination of the fetus, in all multiple congenital anomaly syndromes in which a definitive postnatal diagnosis is not confirmed. These limits were applicable in this study as pathology staff able to undertake the postmortems were limited. Despite this, a definitive postnatal diagnosis was obtained without a postmortem in 40 (80%) cases.

In South Africa, a clinical geneticist is currently not available at all the centres licensed to undertake genetic TOPs. However, we propose that this is not essential and that, given the above figures, this task could be adequately performed by a genetic nursing associate or another clinician, preferably a paediatrician or neonatologist, using a PNAP. Then, when necessary, the information obtained could be reviewed by a clinical geneticist to obtain a definitive postnatal diagnosis for genetic counselling.

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