Postmortem clinical examination by experienced clinical geneticists as an alternative to conventional autopsy for assessment of fetal and perinatal deaths in countries with limited resources

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The aim of this study was to investigate the usefulness of postmortem external examination performed by an experienced clinical geneticist as an alternative to autopsy in countries with limited resources. We studied a consecutive cohort of couples seeking genetic counseling for fetal loss or perinatal death over a period of 3 years. The study involved 230 couples; only 57 of them submitted a fetus or dead neonate, for whom a meticulous postmortem clinical examination was performed by an experienced clinical geneticist. The diagnosis rate for the group of cases subjected to postmortem examination (57.9%) was much higher than that of the group that comprised cases for which diagnosis was made through evaluation of medical records (27.2%).

Whenever fetal or neonatal autopsy is refused or is not feasible, a comprehensive fetal or perinatal postmortem external examination by an experienced clinical geneticist may be a reasonable substitute.

Key words: postmortem examination, fetal loss, perinatal death, congenital malformations, fetal anomalies, prenatal diagnosis, Egypt, autopsy.

The loss of a fetus or a baby soon after birth is emotionally devastating for families and presents many parents with a difficult dilemma. Thus, every effort should be made to identify the etiology of fetal or perinatal death so that appropriate genetic counseling can be offered. Despite the technological advances in antenatal diagnosis and screening, the role of perinatal autopsy in confirming or refuting an antemortem diagnosis is undisputed[1,2]. Therefore, standard autopsy should ideally be an essential part of the full investigation of a fetal loss, stillbirth or neonatal death. The current literature emphasizes the importance of autopsy in providing the accurate etiologic diagnosis necessary for genetic counseling[3-6]. However, the perinatal autopsy rate has steadily declined over recent years [7,8], and an increasing number of parents disapprove of autopsy due to religious objections and emotional reasons, especially in Arab populations. If fetal necropsy is refused, valuable information will be irrevocably lost[9].

In a country with limited resources and inadequate health facilities, such as Egypt, it is not always feasible to provide desirable prenatal or postnatal diagnostic investigations, including autopsies. The majority of hospitals in Egypt, especially in rural areas, do not have access to a specialist perinatal pathologist, by whom this examination should ideally be undertaken according to established guidelines[10]. Additionally, most Egyptian families decline fetal autopsy, probably due to religious, cultural or financial considerations. Regardless of the reason, when a full postmortem investigation is not undertaken, external physical examination by an experienced clinical geneticist could be offered to provide additional clinical information essential for the diagnostic process. External

examination with clinical photographs and plain radiographs is generally affordable and acceptable to most parents.

Therefore, the aim of this study was to investigate the usefulness of postmortem clinical examination as a reasonable and feasible service to improve the genetic counseling offered to families presenting with a fetal loss or perinatal death.

Material and Methods

We scheduled a prospective study of a consecutive cohort of couples seeking genetic counseling for fetal loss or perinatal death over a period of 3 years. All of the families referred for this reason to the Human Genetics Department of the Medical Research Institute of the University of Alexandria, Egypt, were included in the study.

To determine the cause of fetal or perinatal death, we obtained a detailed family history, with construction of the family pedigree, and reviewed the available medical reports, prenatal ultrasound reports and pictures of the dead fetus or neonate. For the families who did not submit the dead fetus or neonate for examination, diagnosis was made through evaluation of the records; all radiographs and clinical pictures of the cases were used.

As for those cases where the dead neonate or fetus was available, whether a spontaneously aborted fetus, one resulting from termination of pregnancy (TOP), a stillbirth or a dead neonate (< 7 days of age), a meticulous postmortem clinical examination was performed by an experienced clinical geneticist. During examination, we recorded the dysmorphic features and congenital abnormalities, if any, by taking clinical photographs for later review, and obtained biometric measurements including length, weight and head circumference. Postmortem radiographs, including whole-body anteroposterior and lateral plain X-rays (fetogram or infantogram), were requested. When the placenta was available, it was sent for histopathological examination.

To evaluate the role of postmortem external examination in facilitating the postmortem diagnostic process and improving genetic counseling, the cases studied were divided into two groups. The first included the couples who submitted their fetuses or dead neonates for postmortem clinical examination. The second group, on the other hand, included the families for whom diagnosis was made through evaluation of the medical records. The diagnostic yield was calculated separately for each of the two groups. The two rates of diagnosis were compared using the chi-square test.

Results

Over the period from January 1, 2011, to December 31, 2013, a total of 230 Egyptian couples came to our department seeking genetic counseling, comprising 77 cases of fetal loss, 103 perinatal deaths and 50 TOP due to abnormal prenatal findings. Almost half of these couples had experienced repeated reproductive loss. About 74% of the couples studied represented consanguineous marriages. Approximately one-third of the families were residents of urban regions, while the other two-thirds lived in rural areas.

During the study period, 57 couples presented their fetus or dead neonate for evaluation. We performed the clinical postmortem examination for 19 cases of fetal loss, 21 TOP and 17 perinatal deaths. For the other 173 couples, genetic counseling was based on prenatal ultrasound (US), medical reports and pictures. Histopathological examination of the placenta, although performed in about 50 cases, did not reveal any placental pathologies.

For the 50 couples seeking genetic counseling after TOP, the most common cause was the detection of NTDs (11 cases; 22%), followed by suspected skeletal dysplasia (12%), Meckel–Gruber syndrome (8%), bilateral renal agenesis (8%) and hydrops fetalis (8%).

The principal causes of fetal and perinatal death among the cases studied were lethal malformation syndromes, single birth defects and unrecognizable patterns of multiple congenital malformations. A known genetic syndrome or congenital malformation(s) was responsible for fetal loss or perinatal death in 60% (138/230) of all the cases studied. Nonetheless, a definite clinical diagnosis could be reached in only 80 cases, with an overall diagnosis rate of 34.8% (80/230). For this group of families, we were able to estimate an accurate risk of recurrence and to offer proper

Table I. Syndromes and Congenital Malformations Detected Among the Studied Fetal and Perinatal Deaths

Single-gene malformation syndromes	27
- Meckel–Gruber syndrome	10
- AR polycystic kidney disease	7
- Fraser syndrome	3
- Lethal multiple pterygium syndrome	2
- Robert's phocomelia	1
- Neu–Laxova syndrome	1
- Walker–Warburg syndrome	1
- Cenani–Lenz syndrome with renal hypoplasia	1
- Epidermolysis bullosa	1
Lethal skeletal dysplasias	21
- Achondrogenesis	3
- Osteogenesis imperfecta, lethal	3
- Short rib–polydactyly, type I	2
- Thanatophoric dysplasia	1
- Kniest dysplasia*	1
- Jeune asphyxiating thoracic dysplasia	1
- Not otherwise specified	10†
Congenital malformations of the nervous system	26
- Anencephaly	9
- Hydrocephalus	8
- Holoprosencephaly	5
- Iniencephaly	2
- Spina bifida & meningeocele	2
Other single birth defects	9
- Bilateral renal agenesis	5
- Congenital heart defects	3
- Duodenal atresia	1
Sporadic disorders	7
- VATER association	1
- Twin-twin transfusion syndrome (acardius acephalus)	1
- Limb–body wall complex syndrome	1
- Agnathia–holoprosencephaly	1
- Gastroschisis and extrusion of the liver	1
- Sacrococcygeal teratoma	1
- Congenital neuroblastoma	1
Unexplained nonimmune hydrops fetalis	14
Unrecognizable patterns of multiple congenital anomalies	34†
No detected anomalies	92

* Kniest dysplasia is not a lethal skeletal dysplasia; however, there is a wide spectrum of disease severity, up to the extent of perinatal lethality.

† The 10 cases of "not otherwise specified" skeletal dysplasia were pooled with the group of unrecognizable patterns of multiple congenital anomalies (34), making a total of 44 cases.

Table II. Distribution of the Cases of Fetal Loss and Perinatal Death Studied, According to the Performance of the Postmortem Examination

Postmortem examination	No. of cases studied	Definite diagnosis	No diagnosis	p-value
Done	57	33 (57.9%)	24 (42.1%)	
Not done	173	47 (27.2%)	126 (72.8%)	<0.0001[ǂ]
Total	230	80 (34.8%)	150 (65.2%)	

[ǂ] Chi-square equals 16.516 with 1 degree of freedom. The two-tailed *p*-value is less than 0.0001. The association between groups and outcomes is considered to be extremely statistically significant.

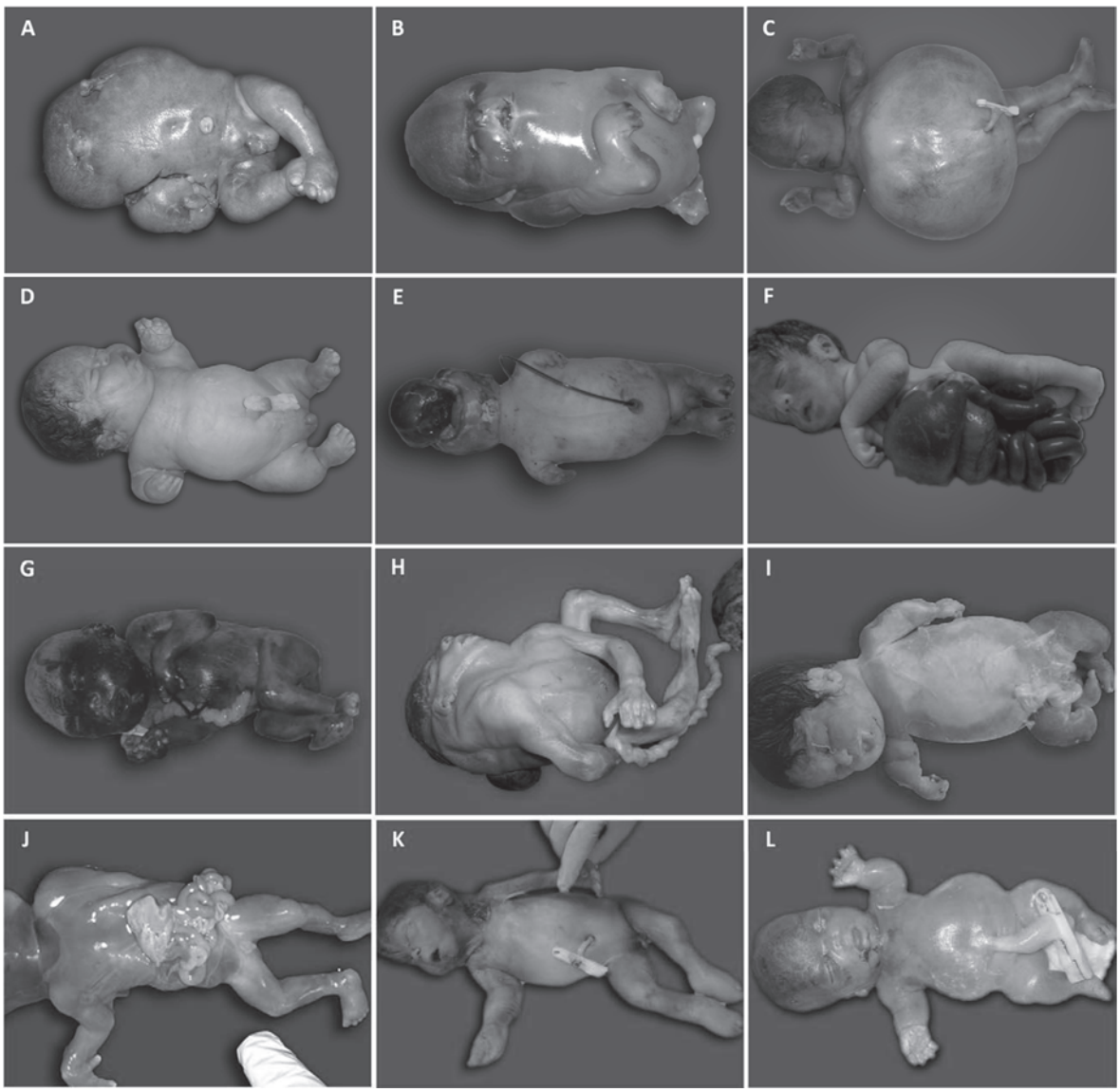

Fig. 1. Postmortem photographs for some of the cases studied: acardius acephalus (twin-twin transfusion syndrome or twin reversed arterial perfusion [TRAP] sequence) [A], a severe case of multiple pterygium syndrome [B], huge abdominal distension in a case of infantile polycystic kidney [C], achondrogenesis type IB [D], frontal encephalocele in Robert's phocomelia [E], limb-body wall complex syndrome [F], Neu–Laxova syndrome [G], iniencephaly [H], a lethal form of osteogenesis imperfecta [I], gastroschisis with extrusion of the liver [J], lethal multiple pterygium syndrome [K] and thanatophoric dysplasia [L].

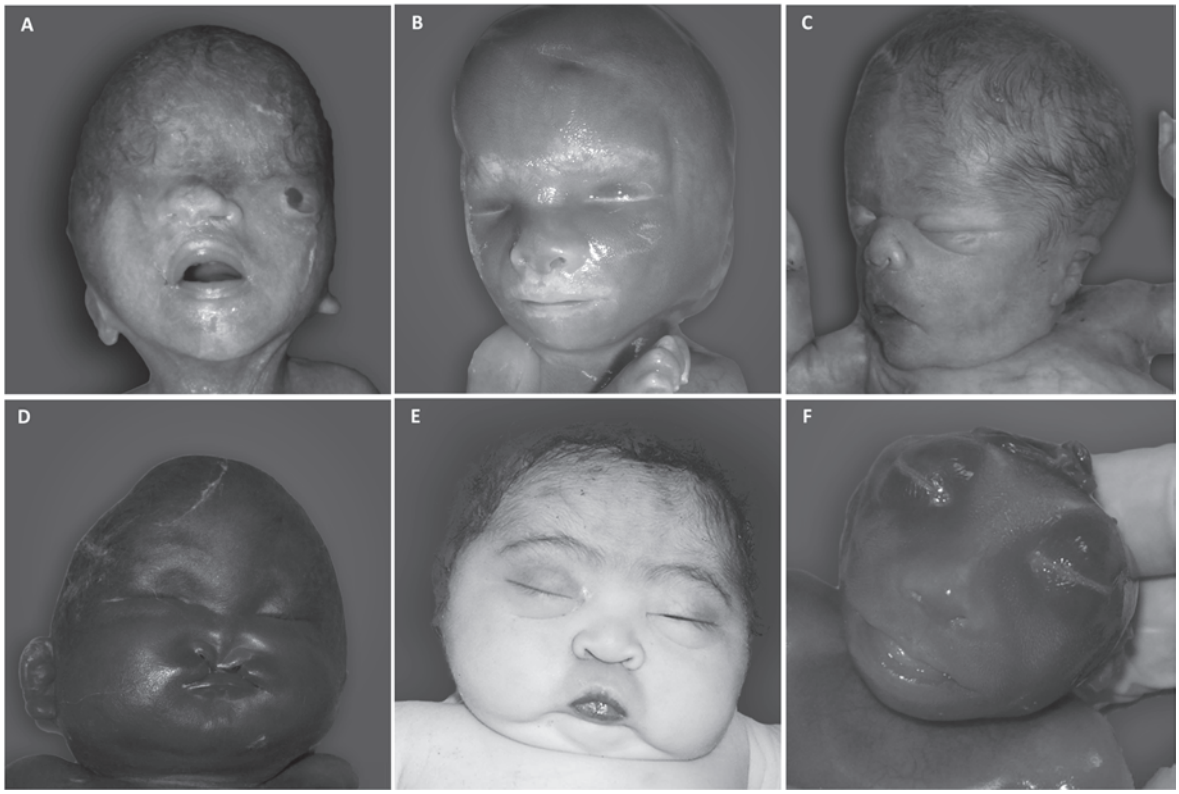

Fig. 2. Postmortem photographs showing the characteristic facial features of some of the syndromes detected: right cryptophthalmos, lateral hair extending to lateral eyebrows, ocular hypertelorism and abnormal nose in a neonate with Fraser syndrome [A], large mouth, broad depressed nasal bridge, anteverted nares, microretrognathia and poorly formed low-set auricles in a fetus with Fryns syndrome [B], characteristic Potter's facies (hypertelorism, deep crease under the eyes, flat nose and low-set, aberrantly folded floppy ears) caused by severe oligohydramnios in a baby with infantile polycystic kidney [C], ocular hypotelorism, cleft nose and median cleft lip in a baby with premaxillary agenesis [D], peculiar round face with mid-face hypoplasia (flat facies), prominent eyes, small mouth and short neck in a neonate with Kniest dysplasia [E], absent cranial vault, absent forehead, "frog-like" eyes, open mouth with protruding tongue and short neck in classic anencephaly [F].

genetic counseling, including the option of prenatal diagnosis when relevant. Table I lists the causes detected for fetal or perinatal death among the studied families, Figures 1 and 2 show postmortem photographs for some of the fetuses and neonates examined, and Fig. 3 comprises postmortem radiographs of cases with skeletal dysplasias.

On the other hand, in 92 cases no detectable malformations were found. For this group, in addition to the 14 cases of unexplained hydrops fetalis and 44 cases with multiple malformations not fitting into any of the recognized syndromes (including 10 cases of "skeletal dysplasia not otherwise defined"), it was impossible to arrive at an exact diagnosis. For all of these couples, we performed karyotyping, which revealed normal results. Even though we were not able to offer these couples a specific recurrence risk, the simple documentation of the malformations could help greatly in genetic counseling and prenatal diagnosis in future pregnancies. For those cases with multiple malformations without a definite diagnosis, the same malformations can be looked for in ultrasound evaluation of subsequent pregnancies.

We then analyzed the diagnostic yield for each of the two groups (those with and without postmortem external examination) separately. A definite diagnosis could be made in 33 of the 57 cases where postmortem examination took place (57.9%). The rate of diagnosis calculated for this group was much higher than the 27.2% rate of the group where no postmortem examination was performed, a difference which was found to be extremely statistically significant (Table II). Accordingly,

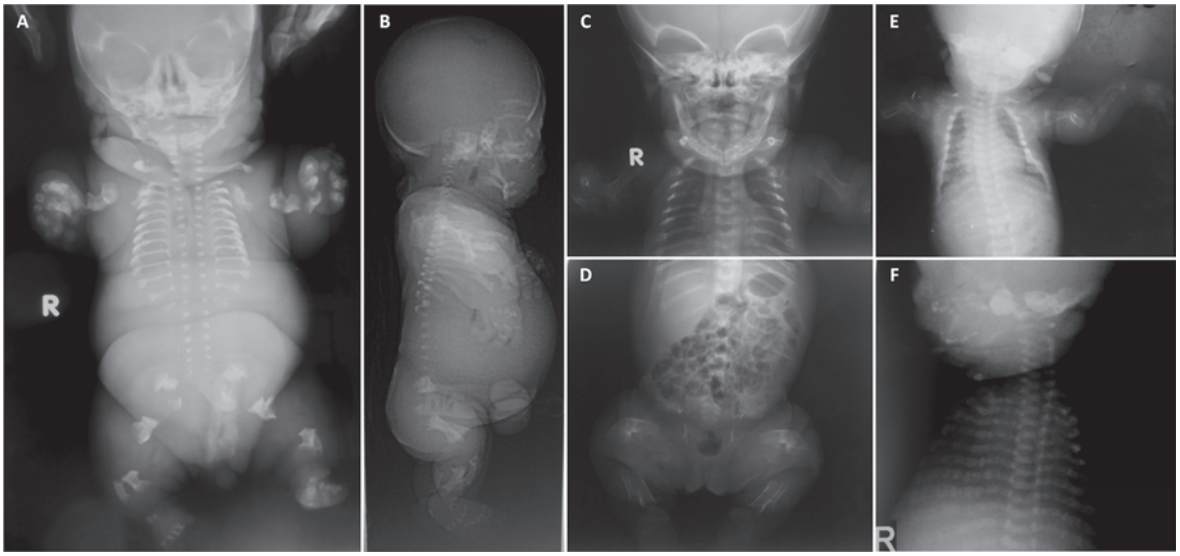

Fig. 3. Postmortem plain radiographs showing some of the skeletal findings detected in achondrogenesis IA [A], thanatophoric dysplasia [B-D] and lethal osteogenesis imperfecta [E&F].

the statistical analysis confirmed the diagnostic value of postmortem external examination and its usefulness for improving the process of genetic counseling.

Discussion

In this study, we investigated a consecutive series of 230 couples with fetal and perinatal deaths; 57 of them subjected their baby to post-mortem clinical examination. Apart from the general purpose of diagnosis, we aimed to assess the diagnostic value of comprehensive postmortem external examination as a potential reasonable substitute for full autopsy. Our results confirmed the diagnostic value of postmortem examination carried out by experienced clinical geneticists, and its usefulness for improving the process of genetic counseling. In the current study, the cause of death was elucidated in 57.9% of the cases subjected to postmortem examination. Surprisingly, this result was comparable to that of fetal autopsy as reported by Sankar and Phadke[11] and Saller et al.[12], with a definite final diagnosis in 59% and 62.3% of fetal deaths, respectively.

Our results indicated that known genetic syndromes and congenital malformations were responsible for 60% of the fetal losses and perinatal deaths in the cases studied. This seemingly high rate for the contribution of genetic causes to fetal and perinatal deaths could be attributed to the fact that the institution where the study was conducted is exclusively a referral center for genetic medicine. Thus, the apparent bias may have been caused by referral of complicated cases. Because our department specializes in genetic disorders, most of the cases referred to us come from high-risk families, such as those who have a baby with birth defects or those with a history of repeated reproductive loss. Generally, the referring obstetricians and perinatologists do not seek genetic evaluation unless no cause for fetal or perinatal death, such as maternal medical disease, obstetric complications, placental abnormalities or immaturity, is evident.

As illustrated in our results, a long list of autosomal recessive lethal syndromes was identified; among them, Meckel–Gruber syndrome and Fraser syndrome were the most common. In light of the very high rate of parental consanguinity observed in this study— ~74%, a figure which is more than the double of that reported for the Egyptian population at large[13]—it was not surprising to find this rate of autosomal recessive disorders. Consanguinity, which is widespread in many countries in our region, increases the prevalence of autosomal recessive diseases at birth. In addition, it is an important correlate of congenital malformations[14].

In the present work, the most frequently detected isolated congenital anomalies were neural tube defects and other central nervous system malformations (11.3%). Our result agrees with that of a previous Egyptian study, which reported central nervous system anomalies as the most common congenital anomalies detected at birth[15]. Most of these cases were correctly identified prenatally. Hence, the prenatal detection of NTDs was the most common indication for TOP in our series (22%), a finding that agrees with several other reports.[11,16,17] Yet, Boyd et al.[18] and Vaknin et al.[19] found that chromosomal abnormalities were the most common cause of TOP, followed by malformations of the central nervous system.

In our case series, generalized edema, cystic hygroma and other features of hydrops were observed in many cases, including those of skeletal dysplasias, structural cardiac anomalies and lethal pterygium syndrome. In 14 cases, however, no obvious cause for fetal hydrops could be identified. The causes of nonimmune hydrops fetalis are numerous, and include chromosomal anomalies as well as hematologic, metabolic and cardiovascular disorders[20-22]. Structural cardiac anomalies, rhythm abnormalities and cardiomyopathies have been reported to account for about 50% of cases [21]. In all 14 of our cases of unexplained fetal hydrops, karyotyping and hematologic tests were done for the parents and revealed normal results. Therefore, a better investigative workup for infections and metabolic disorders would be required to identify other causes of fetal hydrops.

Skeletal dysplasias as a group constituted 19.2% (11/57) of the cases subjected to postmortem examination. The postmortem radiographic findings were of vital importance for establishing the definite diagnosis in these cases (Fig. 3). Previous studies have confirmed that radiographic evaluation is the best method to establish a diagnosis of skeletal dysplasia and may also show small skeletal defects that are difficult to see on dissection[23,24]. On the contrary, the exact specific type of skeletal dysplasia could not be determined in the cases suspected on the basis of prenatal US but no remains were available for postmortem examination and radiography—hence, the report of 10 cases of "skeletal dysplasia not otherwise defined." Despite improvements in the technology, the accuracy of prenatal ultrasound in the specific diagnosis of genetic skeletal disorders remains relatively low[25-27]. Skeletal dysplasias are often difficult to diagnose correctly through prenatal ultrasonography because many of these disorders have similar findings[25]. In order to ensure appropriate genetic counseling, postmortem examination should be done, including clinical examination and radiographs.

The major weakness of this work is that we could not perform karyotyping for the fetuses and neonates submitted due to technical constraints. Since chromosomal abnormalities constitute a significant cause of fetal and perinatal deaths[28,29], special effort should be made to determine the chromosomal status of a dead fetus or a stillborn infant. Unless a better collaborative protocol, based on integration between obstetricians and geneticists, is developed, we will not be able to identify chromosomal abnormalities in cases of fetal and perinatal death.

In conclusion, this study highlights the usefulness of postmortem external examination for improving the process of genetic counseling, since facilities for autopsy are not yet established in Egypt. Our 3-year experience in the performance of a comprehensive postmortem examination clinical evaluation, supplemented with clinical photography and plain X-ray radiographs, proved this process capable of bringing out information that is valuable and necessary for genetic counseling. In fact, this protocol provided a definite diagnosis in 57.9% of the cases, thus giving diagnosis rates comparable to those obtained through full autopsy. Nonetheless, better investigative facilities for chromosomal abnormalities and metabolic disorders will definitely increase the diagnostic yield.

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