Editorial

Does Pakistan Need Foetal Medicine?

In 2013, the Pakistan College of Physicians and Surgeons launched a sub-specialty training programme in Foeto-maternal medicine. The question that has to be asked is: Is the country ready to develop this sub-specialty interest?

Formal training in the specialty of Foeto-maternal medicine is relatively recent, with the first doctor completing sub-specialty training in England in 1992.

Although the first amniocentesis is recorded as being performed in the 19th century to relieve what was presumably gross polyhydramnios, the first amniocentesis performed to identify the foetal sex, based on the number of bar bodies, was not carried out until 1956. The first diagnosis of Down's' syndrome was two years later.

The major driving force behind the development of the specialty has been a desire to tackle specific problems that were perceived to be of major importance. In Great Britain one of the greatest problems was the antenatal detection of the fetus with spina bifida (the incidence of which was higher than in most other countries). Pioneering work by Brooke and Sutcliffe[1] demonstrated the association between raised alpha-Foetoprotein levels and the foetus with a neural tube defect. This led to the identification of raised AFP in the maternal serum and thus biochemical screening arrived. As the usefulness of a raised AFP was on the decline, having been surpassed as a screening tool, by ultrasound, the association of a low AFP as a marker for Down's syndrome was identified. This in turn led to the development of a biochemical screening program for the identification of the foetus with Down's syndrome initially using AFP, Oestriol and HCG.

Another significant problem was the hydropic foetus as a result of rhesus incompatibility. That the foetal anaemia was as a result of rhesus antibodies had been established in 1941. It was however another thirteen years before it was realised that the cause of these antibodies was a transplacental haemorrhage of blood from the foetus to the mother.[2] In 1961, Liley[3] performed the first successful in utero treatment of an unborn child, using x-rays to introduce a catheter into a foetal abdomen in order to be able to perform an intra-peritoneal transfusion. This was to be the mainstay of treatment for this condition for the next 20 years, until Foetoscopic techniques allowed direct access to the umbilical cord. The advent of ultrasound meant that this modality could be used to guide the needle into either the cord or foetal circulation with a significant improvement in both the success rate and a reduction in the foetal loss. In the last century monitoring of rhesus disease was indirect and was based on the assessment of the amount of bilirubin in the amniotic fluid. Today it is non-invasive and achieved by measuring the maximum velocity of blood in the foetal middle cerebral artery.[4] The progress made in treating this one condition highlights the advancement in foetal medicine over the last 50 years. However, at the same time we

have realised that the disease can be prevented by treating sensitising events with prophylactic anti D and more recently by the provision of an additional prophylactic dose of anti D to all rhesus negative women in the early third trimester.[5] Rhesus D disease has nearly been eradicated and transfusion for rhesus D in England is rapidly becoming a rare event.

The Pakistani population has a low percentage of rhesus negativity, and anti D is expensive and is therefore not routinely administered either post childbirth or after a potential sensitising event. This results in significant numbers of women in the country with rhesus antibodies for whom, assuming the husband is homozygous, there will be a worsening potential outcome with each subsequent pregnancy unless they are very fortunate in being able to access one of the few individuals capable of currently performing an intravascular transfusion in the country. Zirbursky and Paul[6] have calculated that in developing countries without a prophylaxis program, the disease results in a 14% stillbirth rate with 50% of survivors dying in the neonatal period or developing cerebral injury.

The rhesus story does not stop here. It is now possible to identify from a maternal blood sample whether or not the mother is carrying a rhesus positive or negative child. As such testing becomes universally available, as the costs of non invasive prenatal diagnosis fall, it will again alter the antenatal management for rhesus negative women.[6] Those women who carry the antibody that have a heterozygous husband will, if they are perceived to be carrying a rhesus negative child, no longer have to go through intensive monitoring throughout the pregnancy. Likewise the antibody negative rhesus negative women found to be carrying a rhesus negative infant will no longer need to be given prophylactic anti D during the course of pregnancy saving this valuable and expensive resource for those who require it.[7]

The greatest leap forward in foetal medicine has to be the introduction of real-time ultrasound scanning. Ultrasound was pioneered by Ian Donald, who was appointed to the Regus Chair of Midwifery in Glasgow in 1954. At the time, ultrasound was being used to assess the quality of welds in the shipbuilding industry. Professor Donald became enthralled with this equipment and used it to scan a variety of tissues demonstrating its potential value in medicine. Ultrasound technology has progressed considerably over the years and we are now able to produce very high quality images of the human foetus. Pregnancies can be identified and the foetal heart visualised four weeks after conception and detailed anatomy of the developing foetus can be studied as early as 10 weeks post conception. This is not without a downside. There are times when an unusual feature generates untold anxiety for the parent in what subsequently turns out to be healthy baby. However ultrasound has enabled us to reliably identify many structural abnormalities at a gestation where it is possible for the parents to make an informed choice about whether or not they wish to continue her current pregnancy.

Unfortunately, although we have the ability to identify many anomalies, at present our ability to successfully treat these is often far more limited. This means that often the options that the parents face are to continue with the pregnancy in the knowledge of the abnormality or to consider a termination of pregnancy. In this situation, for foetal

medicine to be of any significant value, the latter has to be an option and needs to be both socially and morally acceptable.

This does not mean that treatment options will not be available for some conditions in the future. For example, utero-foetal surgery has still to define its role. The foetal conditions that have been at the forefront of foetal surgery are, spina bifida and diaphragmatic hernia. It has long been hoped that in-utero surgery to repair the spinal lesion, as would happen post-delivery, might result in a significantly improved outcome. The current data suggest there may well be some benefit but this has to be measured against the increased morbidity faced by the mother.

Laparoscopic in-utero foetal surgery has the potential to significantly reduce maternal morbidity. A diaphragmatic hernia, with the foetal liver in the chest, diagnosed in-utero, carries a very high risk of foetal death post-delivery, usually as a consequence of pulmonary hypoplasia. The presence of a large amount of bowel in the foetal chest appears to prevent normal lung development. It is possible using ultrasound to assess the size of the developing foetal lungs and make a prediction about the likely mortality risk post delivery. Those with a very high-risk of death may be selected for in-utero therapy. Open surgery for diaphragmatic hernia has long been abandoned. Today the foetoscopic placement of a balloon in the foetal trachea obstructs the usual egress of foetal lung fluid and results in significant lung expansion. Although this technology is still the subject of clinical trials there is some evidence to suggest that such treatment may be beneficial.[8]

Mono-chorionic twins have an approximate 12% risk of developing twin to twin transfusion syndrome. The net result of which is that the recipient twin develops polyhydramnios whereas the donor twin has little or no liquor. Left untreated, this condition carries mortality close to 100% as a result of extreme prematurity. Today the condition can be treated using laser to divide the communicating blood vessels between the two twins. Success is not universal but overall both twins survive in a third of cases and one twin in a further third.[9]

The above are examples of where foetal medicine has made or is making a significant difference in modern obstetric management. However what can it offer in Pakistan? Pakistan's problems are different to those seen in the United Kingdom. Maternal and foetal mortality is significantly higher often as a consequence of lack of resource, little antenatal care, and high parity conditions which have to a large part been overcome in the West. Should resources therefore not be targeted at the provision of high standard of antenatal care for majority in Pakistan rather than the provision of a foetal medicine service for a few.

Certain conditions which have a high prevalence in Pakistan can cause untold morbidity and suffering for the family of the affected child. It is believed that there is a child born with beta thalassaemia major every 90 minutes (personal communication). With access to high-quality medical care, regular reliable and clean blood transfusions and iron chelation these children can have a reasonably high quality of life. However without the above they are likely to be exposed to hepatitis and all the problems associated with iron overload, the net result being significant morbidity and a reduced lifespan. Would it be better to identify the carrier individuals and to offer them prenatal diagnosis in the form of a chorion villus

biopsy at 11 to 12 weeks, with a result available within seven days and an option for termination of pregnancy if the one in four risk of an affected child proved to be the case?

Although gene therapy may be possible in the future, to date, success in this area has been very limited. The concept is logical, with the introduction of healthy genes using viral vectors into the affected foetus. Such treatment remains the Holy Grail as it potentially offers a more acceptable alternative to termination.

The role of the foetal medicine specialist is not to make decisions for the parents but rather to offer the parents choice. Our role is to provide as much information as possible and to impart this to the couple/family in a way that they can understand, in a non-directive manner. We should then provide the options that are available and support the parents in whatever decision that they make.

The provision of a foetal medicine service requires significant infrastructure. This doctor will and does not work in isolation but rather as part of a team which needs to include consultants in genetics, neonatology, paediatric surgery, along with scientists capable of genetic diagnoses to name, but the main players.

One area which needs to be addressed is the problems caused as a result of consanguineous marriages. A recent study based on newborn babies[10] in Bradford, Yorkshire, in the UK, which has significant number of Pakistani families, reported a 6% excess in congenital anomalies in consanguineous families when compared to those which were not. This is a rate over double that seen in the non-consanguineous couples. Many of these conditions are lethal and account for the increased neonatal mortality seen in this population. It is not foetal medicine's role to denounce consanguinity or to blame this coupling for the outcome; however the increased risks need to be explained, preferably before the marriage is arranged. Taboos need to be broken so that, for example, in families where it is known that thalasaemia is prevalent, consideration is given to carrier testing before the partners are chosen. Such a policy has been successfully utilised in the Jewish population to avoid Tay Sach disease.

I have been coming to Pakistan for the last 20 years, teaching invasive procedures, ultrasound and some of the theory behind foetal medicine. Over that time I have seen a significant mood change in favour of foetal medicine within the country. Personally I'm delighted that the College has launched a sub-specialty training programme in Foeto-maternal medicine in order to decrease peri-natal mortality. I believe that now is the time for foetal medicine to become established within the country and I wish all those involved, every success.

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