INTRODUCTION
Fraser Syndrome (FS) is a rare autosomal recessive disorder characterized by cryptophthalmos (CO), syndactyly, and urogenital defects. It has a reported incidence of 0.043 per 10,000 live births and 1.1 in 10,000 stillbirths. George Fraser first described it as a complex disorder with multiple anomalies and named it 'cryptophthalmos syndrome'. CO is not a regular feature of this syndrome; hence, the eponym 'Fraser syndrome' is preferred. FS is genetically heterogeneous; so far mutations in FRAS1, FREM2 and GRIP1 genes have been linked to FS. FS can be diagnosed on clinical examination, pre-natal ultrasound or perinatal autopsy. We present a case of a 3 months old child born to consanguineous healthy parents with bilateral complete CO, unilateral microphthalmia, hypertelorism, syndactyly (hands and feet bilaterally), ambiguous genitalia with cryptorchidism and an umbilical hernia. We also present the criteria for diagnosing FS and the significant features on pre-natal ultrasonography. Around 200 case reports of patients with FS and CO have been published. To our knowledge, this is the first reported case of FS in Pakistan.

CASE REPORT
A 3 months infant was brought to us by his parents with complaints of skin covering his eyes. The infant was born to consanguineous healthy parents, the product of their sixth pregnancy. The baby was born at term by vaginal delivery at home following a normal pregnancy. Infant's birth weight was 2.2 kg. Parents belonged to a low socioeconomic background with limited access to medical facilities. No pre-natal record was available. All the previous children are normal with no dysmorphology. There was no family history of any congenital anomalies. The mother had one miscarriage before this baby at 12 weeks of gestation.

On clinical examination, the infant did not respond to intense light stimulus. There was complete CO bilaterally with no evidence of eyelids or eyelashes. Eyebrow was partially formed on the right but ill demarcated on the left side. The right globe was large and cystic on palpation. The left globe was adherent to the overlying skin and microphthalmic (Figure 1a). Hypertelorism was also present. The nasal and oral passages, ears and facial features were normal.

INTRODUCTION
Fraser Syndrome (FS) is a rare autosomal recessive malformation characterized by cryptophthalmos (CO), syndactyly, laryngeal and urogenital defects. It has a reported incidence of 0.043 per 10,000 live births and 1.1 in 10,000 stillbirths. George Fraser first described it as a complex disorder with multiple anomalies and named it 'cryptophthalmos syndrome'. CO is not a regular feature of this syndrome; hence, the eponym 'Fraser syndrome' is preferred. FS is genetically heterogeneous; so far mutations in FRAS1, FREM2 and GRIP1 genes have been linked to FS. FS can be diagnosed on clinical examination, pre-natal ultrasound or perinatal autopsy. We present a case of a 3 months old child born to consanguineous healthy parents with bilateral complete CO, unilateral microphthalmia, hypertelorism, syndactyly (hands and feet bilaterally), ambiguous genitalia with cryptorchidism and an umbilical hernia. We also present the criteria for diagnosing FS and the significant features on pre-natal ultrasonography. Around 200 case reports of patients with FS and CO have been published. To our knowledge, this is the first reported case of FS in Pakistan.

DISCUSSION
A primary defect of apoptosis has been suggested as the cause of FS, since several of the anomalies result from failure of programmed cell death. Mutations in FRAS1 and FREM2 (4q21) have been implicated. MOTA (manitoba-oculo-tricho-anal) and BNAR (bifid nose, renal agenesis and anorectal malformations) syndromes have also been linked with mutations of FREM1 gene. A mutation(s) in GRIP1, which encodes a scaffolding protein that interacts with Fras1/Frem proteins, has recently been associated with FS. In the remainder of cases, it may be supposed that mutant alleles of other genes, not as yet identified, are to blame.
CO (hidden eye behind an unopened eyelid) is a rare disorder where the eyelids are fused. It is often bilateral and symmetric. It is divided into three types; complete, incomplete, and abortive. The complete variety is the most common. The eyelids do not form and the eyelid skin grows continuously from the forehead to the cheek. The globe is generally abnormal with absence or poor development of the ocular adnexa. The incomplete variety presents with facial skin fusing to the medial aspect of the globe with some eyelid structures present laterally. In symblepharon or abortive CO, the upper eyelid skin fuses to the superior portion of the globe, thus forming the anterior layers of the cornea.

Anterior segment abnormalities associated with FS include corneal clouding, sclerocornea, microphthalmia, microcornea and anophthalmia that could possibly be confused with Peters’ plus or Walker-Warburg syndrome.

Diagnostic criteria for distinguishing between isolated CO and FS were provided by Thomas et al. and most recently the diagnostic criteria were revised by Van Haelst et al. Diagnosis of FS can be made if 3 major criteria; or 2 major and 2 minor criteria; or 1 major and 3 minor criteria are present (Table I). In this case, we have CO, syndactyly and abnormal genitalia as three major criteria and umbilical hernia as the minor criterion.

Consanguinity has been found in families with more than one affected child, estimated to be around 15 - 25%. CO is present in 85 - 93% of the cases (unilateral 25 - 28%, bilateral 45 - 48%), syndactyly in 54 - 58%, laryngeal anomalies in 21 - 31%, genital malformations in 17 - 31% and renal agenesis in 23% of the cases. Twenty five percent of the affected infants are stillborn, whereas 20% die before the age of one year because of hyperechoic lungs and complete renal agenesis as oligohydramnios. Other ultrasonographic features that are highly suggestive are CO, microphthalmia, facial asymmetry, syndactyly and obstructive uropathy.

A high maternal serum alpha-fetoprotein level also increases the suspicion of FS. In families with a previously affected child or in cases of previous still-birth due to renal or laryngeal anomalies, it is vital that mothers undergo a detailed antenatal ultrasound at 14 - 16 weeks.

The ocular management of FS is complex and multifaceted. The urgency of surgery depends on the presence of any visual potential and the degree of exposure keratopathy. In cases of complete CO, there is slim possibility of gaining useful vision even with surgery; however, if electrodiagnostic tests infer that there is visual potential, surgeon(s) may feel obligated to intervene in order to salvage some vision. In cases of incomplete and partial CO, results of surgery depend on the degree of lid involvement and the integrity of the underlying ocular tissue. Cornea requires urgent treatment from birth to avert exposure keratopathy. The eyelids can be reconstructed with mucous membrane grafts in combination with local mucocutaneous or eyelid sharing grafts such as pedicle rotation flaps or Mustarde switch flaps. Moreover, the underlying globe must be reconstructed which entails dissecting the corneal adhesions from keratinized cornea, membrane grafts to the globe and keratoplasty. The success of complex lid reconstruction is limited by defective tear production, lack of healthy conjunctiva and by underlying defects like anterior segment dysgenesis. Furthermore, delivery of anaesthesia and its complications have to be evaluated pre-operatively.

A pre-natal diagnosis is imperative for guiding parents regarding prognosis, management and for genetic counselling for future pregnancies. In utero gene therapy may ultimately be the final frontier of this potentially fatal autosomal recessive disorder.

REFERENCES


