Placental chorioangioma with an emphasis on rare giant placental chorioangioma and associated maternal and perinatal outcome: Clinicopathological study in a single centre

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ABSTRACT

Context: Giant placental chorioangiomas (GPC) are exceedingly rare and harbour potential to cause feto-maternal complications with resultant morbidity. Aims & Materials and Methods: A retrospective study using details from Department of Obstetrics & Gynaecology and Pathology is done to study the various clinical and pathological features of placental chorioangiomas with a special emphasis on the rare GPCs and associated complications. Results: Over a period of 16 years, 20 cases were diagnosed as chorioangioma in our institution. 60% of these occurred in primigravida (n=12) and 71% cases carried a female foetus. Only 25% cases were > 30 years. Maternal and foetal complications occurred in 85% and 50% cases. Pre-term labour was the common maternal complication and foetal death/stillbirth was the most common foetal complication. There were 15 cases of GPC, 73% occurred in primigravida (n=11) and 75% of cases carried a female foetus. There were no cases of maternal death or recurrence. Primigravida was associated with maternal complication in contrast to multigravidity (P = 0.049). Mean age of mothers with maternal complications and those without maternal complications reached statistical significance (P = 0.001). Though histologically all the cases were similar, calcification and infarction were seen exclusively in GPC cases. Conclusion: GPCs are rare and our data adds evidence to use 4cm as an optimum cut-off in the definition. GPCs were associated with a high percentage of primigravidity, female foetus, and poorer outcome of pregnancy. Routine examination of placenta in unexplained foetal/perinatal demise must be stressed to detect microscopic evidence of chorioangioma.

Keywords: Chorioangioma, giant chorioangioma, haemangioma, non-trophoblastic, placental tumour

Introduction

Chorioangioma of placenta is a benign tumour that originates from the chorionic tissue owing to proliferation of chorionic vasculature. These tumours are uncommon in practice with prevalence ranging from 0.1% to 1% of pregnancies[1-4]. Although incidentally detected by antenatal Ultrasonography (USG) examination, many authors believe that the true prevalence remains unknown since most lesions remain undetected owing to their small and innocuous size[2,5-7]. As a result, most gestations remain asymptomatic and uneventful with subsequent histological examination of the expelled placenta revealing the
presence of this inconspicuous tumour. At least one USG is recommended as a part of routine antenatal care, wherein, the details of foetus, liquor and placenta are noted. Documentation of placental location and morphological appearances are done. Any abnormal finding such as hemorrhage, presence of cyst or mass should be described in detail and reported.

As the scans are performed by both sonologists/obstetricians, placental mass are being detected; however, primary health care provider should also be aware of these incidental findings and should intervene accordingly. The size of the mass and presence of foetal hydrops are main determinants of poor perinatal outcomes which will impact on the pregnancy management like frequent visits and the need for foetal monitoring.

Giant placental chorioangiomas (GPC) are exceedingly rare with literature revealing mainly case reports and very few case series. There is a paucity of published literature from India and this study represents the largest series from the Indian subcontinent describing various clinical and pathological features of placental chorioangioma with a special emphasis on the rare GPCs and the associated foetal and maternal complications.

Materials and Methods

This study was approved by the Institutional Review Board and Ethics Committee (IRB Min No 10613).

Cases were retrieved from the archives of Department of Pathology and from a tertiary care centre. The study material included data over a period of 16 years (from January 2001 to June 2017). Clinical characteristics like age, status of gravidity, parity, preexisting comorbidities, gestational age, natural course of pregnancy, foetal and neonatal details were all obtained from the medical records in the Department of Obstetrics and Gynaecology, from a tertiary care centre. Haematoxylin and Eosin (H&E) stained glass slides and formalin-fixed paraffin embedded (FFPE) tissue blocks were retrieved and reviewed.

Statistical analysis

Frequency and percentages were used for categorical variables. Mean with standard deviation was used for continuous variables. Chi-square and Fisher exact probability test were used to test the associations between maternal and foetal complications and with clinic-pathological characteristics and variables. Independent t-test was used for age with clinical parameters. Statistical analysis was performed using STATA 13.0 version software.

Results

Over the past 16 years, a total of 1295 placentas have been subjected to histopathological examination in our institution. A diagnosis of chorioangioma was made in 20 cases, with a prevalence of 0.015% in our study. These 20 cases included 16 cases of chorioangioma and 4 cases of chorioangiomatosis. There were no cases of chorioangioma in our study.

Placental chorioangioma and feto-maternal correlation

The maternal age at diagnosis of chorioangioma in our study ranged from 20 to 33 years with a mean age of 25.4 years (SD ± 5.6). About 10 cases were less than 25 years of age and similarly 10 cases were more than 25 years of age. Only 1/4th (n = 5) of the cases were older than 30 years.

In total, 60% of the cases were Primigravida (n = 12) and 40% were Multigravida (n = 8), out of which 17 cases were suspected to have a placental space occupying lesion by antenatal USG examination [Figure 1]. There were no cases of multiple/twin pregnancy.

In this study, gender of foetus/neonates was documented for 17 cases and had 12 girls (71%) and 5 boys (29%). There were 2 cases (diagnosed in 2001, Case #1 and Case #3) for which gender of child could not be traced in the records and 1 case (Case #12) had a missed abortion at 13 weeks of gestation.

Maternal complications were seen in 17 out of the 20 cases (85%). Among all the various maternal complications that were seen associated with chorioangioma in our study [Tables 1 and 2], preterm labour was found to be the most common.

Foetal complications were seen in 10 cases (50%) that included Intrauterine death (IUD), intrauterine growth retardation (IUGR), low birth weight (LBW), non-immune hydropsfoetalis and stillbirth. There were no maternal deaths associated with chorioangiomas in our study. None of the cases in our study had a recurrent chorioangioma or any distant metastasis.

GPC and feto-maternal correlation

Using a 5-cm cut-off, there were 14 cases of GPC; however, when 4 cm cut-off was used, an additional case was added resulting in a total of 15 cases of GPC. The mean age was 25.3 (SD ± 3.1) years and the age range was 20 to 32 years. Out of the 15 GPC cases, 11 occurred in primigravida’s (73%), whereas 4 occurred in multigravidas (27%).

Figure 1: Ultrasound B mode picture of hydrops and placental mass Large chorioangioma of 10x10cm well circumscribed mass extending beyond placental margin
Vig, et al.: Pregnancy outcomes in women with chorioangioma

Gender of the foetus/neonates was documented in 12 out of these 15 cases that included 9 girls (75%) and 3 boys (25%). Maternal complications were seen in 93% of cases with GPC (n = 14) and included polyhydramnios, preterm labour, preterm premature rupture of membranes, preeclampsia, placental abruption, hemolysis, elevated Liver enzymes, low platelets (HELLP syndrome), gestational diabetes mellitus (GDM) and missed abortion. Preterm labour was the most commonly encountered maternal complication in this group.

Foetal complications were marginally more (n = 8) with complication in 60% of the foetus with GCP as against 50% in chorioangioma group. The complications included 2 cases of stillbirth, 2 cases of IUD, 1 case of missed abortion at 13th week of gestational age and 3 cases of IUGR and LBW babies. All the 3 cases with IUGR and LBW babies had favourable outcome in the post-natal period and are alive.

There were no cases of maternal death associated with GPC in our study.

Table 1: Demographic and clinical presentation in chorioangioma cases

| Case No. | Maternal age (years) | Gravidity and Gestational age | Diagnosis | Tumour size (cm) | Singleton/Twin pregnancy | Gender of fetus | Maternal complication | Foetal complication |
|----------|----------------------|-------------------------------|-----------|------------------|--------------------------|----------------|----------------------|---------------------|
| 1        | 20                   | Primigravida                  | Chorangioma | 9×6×3            | Single                  | NA             | Abruptio placenta    | NA                  |
| 2        | 22                   | Primigravida, 32+3 weeks      | Chorangioma | 8×8×6            | Single                  | Girl           | Polyhydramnios, Preterm labour | IUGR, LBW |
| 3        | 28                   | Primigravida; preterm         | Chorangioma | 8×6×5            | Single                  | NA             | Preterm labour       | Stillbirth |
| 4        | 24                   | Multigravida, 38+5 weeks      | Multifocal chorangiomas/chorangiomatosis | 3 cm | Single | Girl | LSCS, Gestational HTN | None |
| 5        | 30                   | Thrombophilia case, Multigravida, 38 + 2 weeks | Focal chorangiomatosis | Not seen on gross | Single | Boy | None | None |
| 6        | 33                   | Multigravida, Previous Molar pregnancy, 39 + 1 weeks | Chorangioma | 0.7 | Single | Girl | None | None |
| 7        | 25                   | Primigravida, 37 + 2 weeks    | Chorangioma | 9×7×1            | Single                  | Boy            | Abruptio placenta, Preeclampsia, HELLP syndrome, Emergency LSCS | None |
| 8        | 32                   | Primigravida, Term placenta, delivered at 29 weeks | Chorangioma | 8×8×3.5          | Single                  | Girl           | None | None |
| 9        | 20                   | Primigravida, delivered at 29 weeks | Chorangioma | Not seen on gross | Single | Girl | Preterm labour | Stillbirth |
| 10       | 31                   | Primigravida, 29 weeks        | Chorangioma | 5.5×3.1×2.5      | Single                  | Boy            | Preterm labour       | IUGR, LBW |
| 11       | 22                   | Primigravida, 32 + 6 weeks    | Chorangioma | 8.3×6×4          | Single                  | Girl           | Preterm labour       | IUGR, LBW |
| 12       | 21                   | Multigravida, 13 + 5 weeks with missed abortion | Diffuse chorangiomatosis | 5×4×2 | Single | Abortion (NA) | Missed abortion | Abortion/death |
| 13       | 23                   | Primigravida, 37 weeks        | Chorangioma | 8×5×3            | Single                  | Girl           | Gestational DM       | None |
| 14       | 27                   | Primigravida, 37 + 6 weeks    | Chorangioma | 9×9×4            | Single                  | Girl           | Gestational DM       | None |
| 15       | 22                   | Primigravida, 38 + 1 weeks    | Chorangioma | 5×3.5×5          | Single                  | Girl           | Gestational DM       | None |
| 16       | 26                   | Primigravida, 31 + 4 weeks    | Chorangioma | 16×8.5×4         | Single                  | Girl           | Gestational DM       | IUD death |
| 17       | 27                   | Multigravida, 24 weeks        | Chorangioma | 4.7×3.6×3.5      | Single                  | Boy            | Polyhydramnios, Preterm labour | Stillbirth |
| 18       | 21                   | Multigravida, 28 + 6 weeks    | Multple chorangiomas | 0.5-3.2×2.5×2 | Single | Boy | Severe Pre-eclampsia, Preterm labour | IUGR, LBW |
| 19       | 30                   | Multigravida, 32 weeks        | Chorangioma | 7.9×6.8×5.3      | Single                  | Girl           | Polyhydramnios, PPROM, Preterm labour | Hydrops fetalis |
| 20       | 24                   | Primigravida, 35 + 3 weeks    | Chorangioma | 9.8×8.7×6.5      | Single                  | Girl           | Polyhydramnios, Preterm labour | None |

Table 2: Chorangioma versus giant placental chorangioma cases distribution

| Criteria                        | All chorangioma cases (n=20) | (n=15) |
|---------------------------------|-------------------------------|-------|
| Mean maternal age (years)       | 25.5 (SD±5.6)                 | 25.3 (SD±3.1) |
| Maternal age (years)            |                               |       |
| <25                             | 50%                           | 47%   |
| 25-30                           | 25%                           | 33%   |
| >30                             | 25%                           | 20%   |
| Primigravida                    | 60%                           | 73.3% |
| Multigravida                    | 40%                           | 26.7% |
| Gender of fetus/neonate         |                               |       |
| Girl                            | 71%                           | 75%   |
| Boy                             | 29%                           | 25%   |
| Maternal complications          | 85%                           | 93.3% |
| Foetal complications            | 50%                           | 60%   |
| Foetal/perinatal death          | 30%                           | 33.3% |

Gender of the foetus/neonates was documented in 12 out of these 15 cases that included 9 girls (75%) and 3 boys (25%). Maternal complications were seen in 93% of cases with GPC (n = 14) and included polyhydramnios, preterm labour, preterm premature rupture of membranes, preeclampsia, placental abruption, hemolysis, elevated Liver enzymes, low platelets (HELLP syndrome), gestational diabetes mellitus (GDM) and missed abortion. Preterm labour was the most commonly encountered maternal complication in this group.

Foetal complications were marginally more (n = 8) with complication in 60% of the foetus with GCP as against 50% in chorioangioma group. The complications included 2 cases of stillbirth, 2 cases of IUD, 1 case of missed abortion at 13th week of gestational age and 3 cases of IUGR and LBW babies. All the 3 cases with IUGR and LBW babies had favourable outcome in the post-natal period and are alive.

There were no cases of maternal death associated with GPC in our study.
Statistical analysis

Primigravidity was associated with maternal complication in 70% of cases as compared with multigravidity (29%), which was statistically significant ($P$ value = 0.049).

Our data also shows that there is any statistically significant correlation neither between tumour size and maternal complications ($P$ value = 0.07) nor between tumour size and foetal complications ($P$ value = 0.60).

Moreover, our data show no statistically significant correlation between gravidity and foetal complications ($P$ value = 1), gender of foetus and maternal complications ($P$ value = 0.87) or gender of foetus and neonatal complications ($P$ value = 0.47).

The average age of mothers with maternal complications (24.3 years) and without maternal complications (31.6 years) was found to be statistically significant ($P = 0.001$).

Histopathological examination

The gross dimension of the tumours ranged from being microscopic (not seen on gross examination of placenta) to 16 cm in maximum dimension. The grossly visible tumours were spherical with a lobulated and smooth external surface [Figure 2]. All of the grossly visible tumours were well circumscribed and showed a uniformly haemorrhagic, tan-brown, bulging, soft cut surface. Tumours were present on the maternal surface of placenta in 6 cases, foetal surface in 6 cases and 4 cases showed tumour located within the placenta. Two cases were diagnosed microscopically and were not seen at the time of gross examination. Four cases showed multifocal tumours (chorioangiomatosis) and remaining 16 were solitary tumours. Case #17 had multiple small tumours over the foetal surface that resembled vesicles and was masquerading radiologically as a partial mole during the USG exam.

Microscopy

All the 20 cases of chorioangioma in our study were of the Angiomatous/capillary pattern. All the tumours were unencapsulated but well-circumscribed, arranged in a vague lobular architecture or as sheets composed of tiny congested vascular channels that were lined by plump endothelial cells [Figure 3]. There were no mitotic figures, any significant cytological atypia or architectural complexity.

A total of 7 cases showed foci of infarction and scattered specks of calcification were seen in 2 cases. An interesting finding of note was that features like calcification, infarction and fibrin deposition (seen in 9 cases) were seen exclusively in the giant chorioangiomas and were consistently absent in the chorioangiomas smaller than 4 cm in size. The adjacent placenta showed no evidence of abnormal trophoblastic proliferation or any other significant lesion.

Discussion

Tumours of the placenta are uncommon and from a practical view can be classified as either trophoblastic or non-trophoblastic. Chorioangioma is an indolent tumour, within the non-trophoblastic category, that arises from chorionic mesenchyme and is composed of benign proliferation of small calibre vascular channels.1-8 The rarity of these tumours was elicited by a prevalence of 0.01% in our study, which is lower than the rate of 0.16% to 1% as reported by a few studies in the literature.1-4 This article represents the first large scale study on placental chorioangioma from the Indian subcontinent.

Age

The maternal age at diagnosis of chorioangioma in our study ranged from 20 to 33 years with a mean age of 25.4 years (SD ± 5.6) that is similar to the report by Bashiri et al.7 but, younger than the 30.6 reported by Wou et al.4 and 32 reported by Theresia et al.13 Unlike Guschmann et al.,1 who studied 136 cases of chorioangiomas, 50% of our cases were below 25 years of age which is twice the percentage seen in their series (24.3%). Our data also differs from theirs with regard to the fact that only 25% of our cases were older than 30 years, while their series observed 46%. Some authors suggest that incidence of chorioangioma increases with maternal age and
found association with elderly primigravida, but this feature was not confirmed by our study. The eldest primigravida in our series was 31 years old.

**Gravidity**

Our study shows that chorioangiomas are seen more in primigravidas, a finding that has also been observed in other studies.[1,4] We found that GPCs also occur more frequently in primigravidas (73%); however, this feature needs to be confirmed by further studies. There are reports that describe chorioangioma and GPC to have a higher incidence in twin/multiple pregnancies; however, all 20 cases in this study were singleton pregnancies.[13]

**Gender of foetus/neonate**

Various studies and case reports mentioned a higher incidence of placental chorioangioma in pregnancies carrying a female foetus, and the findings in our study are concordant with these published literatures.[1,4,8,14] Similar to the higher percentage (89%) observed by Wou et al.[14] in their cohort of large chorioangiomas associated with female foetus, our data also shows higher incidence (75%) with the female foetus.

**Maternal complications**

We observed maternal complications in 85% of cases. Among all the various clinical complications that have been observed in literature, correlation of chorioangiomas with polyhydramnios and preterm labour appears to be quite significant.[2,3,8,11-13] The most common maternal complication in our study population was preterm labour. This was in contrast to polyhydramnios in the study by Wu et al.[11] Higher percentage (93%) of maternal complications was evident in the GPC group; again preterm labour was most common.

Polyhydramnios was seen in 20% of our series, and correlated with the reported incidence (14%-36%) by some studies; however, it was much higher than the 0.7% reported by Guschmann et al.[3,8,14] GPCs behave as potential arteriovenous shunts resulting in a hyperdynamic circulation for the dependant foetus that subsequently compensates by high urine volume or may result in direct fluid transudation from the placental surface. Preterm delivery is also suggested to be direct sequelae of polyhydramnios. This feature was also validated in our study, since all the 4 cases of GPC that had polyhydramnios had concomitant preterm labour.

We believe the high percentage of maternal complications in our study may be attributed to perhaps the selection bias in our study. Unlike some of the other studies wherein, as an institutional policy, all placentas are sent to the pathology laboratory for routine examination, we receive placentas from only complicated pregnancies/labours in our high-volume tertiary-care institute, with a clinico-radiological suspicion of placental pathology.

Of note was the presence of GDM which was seen in 4 cases, all of which were GPC cases. Guschmann et al. found gestational DM in 6.5% of their cases and Wou reported 4.4% in their study, but none were seen in GPC cases.

The incidence of preeclampsia and HELLP syndrome (1 case) in our study is lower than that of Guschmann and Wou et al.[1,4] (13.2% and 11%, respectively). Interesting to note was the higher incidence of maternal complications seen with primigravidas in contrast to multigravidas which reached statistical significance (P value = 0.04).

Moreover, our data also show that the mean age of mothers who developed maternal complications (24.3 years) as compared with those who did not develop any maternal complications (31.6 years) was statistically significant (P value = 0.001).

**Foetal complications**

Any pathology of the placenta has a potential to cause adverse effects on the dependent foetus and many previous reports have studied the relation between chorioangiomas and associated foetal distress. About 50% of our cases developed foetal complications while the GPC group observed a slightly higher percentage (60%). These findings are also corroborated by the existing literature,[3,5,7,8] apart from the study by Zanardini et al.[9] where foetal complications were seen in 95% cases of GPC. Despite these figures and fortunately too, not all the cases of GPC had an adverse outcome, as observed by some authors.[17,18]

Only 1/3rd of the GPC cases had foetal death/stillbirth and the remaining 2/3rd had a favourable outcome. All cases of smaller chorioangiomas did not have a favourable foetal outcome either. One case had an IUD. IUGR/LBW was seen in 3 cases (2 GPC and 1 case with multifocal chorioangiomas). Complications may arise due to the chronic hypoxic environment, when large chorioangiomas deprive and shunt oxygenated blood away from the utero-placental-foetal circulation. Literature also suggests that pooling of red blood cells and platelets within chorioangiomas can lead to microangiopathic haemolysis and lead to foetal anaemia, thrombocytopenia, distress and death.[7,9,14,19] Non-immune hydrops foetalis is rarely seen in association with chorioangiomas[9,20] and we observed 2 such cases in our study.

With the continuous improvement in medical imaging modalities and regular antenatal screening programmes, placental pathologies can be detected earlier and guide management. The advent of Doppler imaging and magnetic resonance imaging (MRI) have added to our arsenal as they are safe and offer additional information for personalised assessment and antenatal management.[21,22] USG shows chorioangioma as a well-circumscribed and richly vascular mass with hypo/hyperechoic areas and is clearly demarcated from the adjacent placenta. Increased blood flow as seen by Colour Doppler imaging can be used to differentiate chorioangioma from other placental lesions.[23,24] In our centre, USG imaging detected placental chorioangiomas during antenatal scans and none of our cases had an MRI. Although MRI is safe during pregnancy and provides additional anatomical details, it may not prove to be...
cost-effective, and hence is not the standard imaging modality. USG provides almost similar results, is cheaper, easily available and time saving.

Pathological features

Literature shows that majority of chorioangiomas are microscopic and in one study, 60% cases were diagnosed exclusively by histopathological examination. In our data, tumour dimension ranged from microscopic (2 cases) to the largest, 16 cm. Although the grossly visible tumours are usually seen on the foetal surface, we observed an equal distribution (6 cases each over the maternal and foetal surfaces). Gross appearance of both the small and GPC are similar to haemangiomas seen elsewhere in the soft tissues, with a congested fleshy cut surface. Histologically, all our cases were capillary/angiomatous, and, as shown by literature, histological subcategorisation carries no clinical significance. These tumours are essentially an intricate network of small blood vessels, causing shunting of blood, depriving the foetal circulation of its crucial blood supply and subsequently creating a ‘physiological dead space’.

None of our cases showed any sinister histological features. An atypical cellular chorioangioma has been described, however, no case of distant metastasis has ever occurred.

A unique feature that emerged was the presence of calcification, fibrin deposition or infarction, which was exclusive to GPC. This feature has not been studied previously and may perhaps have a causal association with the high percentage of feto-maternal complications that was seen with GPC cases.

There is little agreement in the literature regarding a suitable ‘cut-off’ for GPC. Some believe tumours more than 4 cm are clinically significant while some prefer using a 5-cm cut-off. In our study, we used the 4 cm mark and found foetal/neonatal death to occur in 33.3% cases. A comprehensive systematic literature review of 112 chorioangiomas showed tumours measuring more than 4 cm were associated with foetal/neonatal demise in 27.7% cases. Moreover, none of the cases smaller than 4 cm resulted in foetal death.

Paucity of cases precludes any definite treatment guidelines for chorioangioma or its associated complications. Drainage of the amniotic fluid for polyhydramnios, intrauterine foetal blood transfusions, endoscopic laser coagulation, microcoilembolisation and electrosurgery are emerging as recent interventions; unfortunately, these are all high-risk procedures with quite variable success rate. In our study, all the patients were managed conservatively and the decision to deliver the foetus was dependant on individual assessment of maternal and foetal risks. Literature review by Al-Wattar et al also failed to demonstrate the benefit of any active intervention over conservative management in order to improve foetal/neonatal mortality.

Conclusion

Our data show that both the rare placental chorioangioma and even rarer GPCs occur more frequently in primigravidas and female foetus, with no definite correlation with maternal age. Although GPCs have a high percentage of feto-maternal complications, fortunately majority have a favourable outcome; however, 33% foetal/neonatal mortality rate calls for thorough antenatal ultrasound examination to detect these tumours and initiate timely management of pregnancy to ensure a favourable outcome. Routine histopathological examination of placenta should be emphasized to detect microscopic evidence of chorioangioma, especially in cases with unexplained complications.

Key messages

1. The primary physician or health care provider should wisely decide on need for close surveillance or immediate intervention. Proper counselling and reassurance is of paramount importance.
2. Follow-up of the choriangioma size and presence of associated foetal findings will determine the outcome and hence management should be individualised.
3. Over diagnosis and wrong interpretation can lead to inconvenience of frequent visits and financial burden especially in low resource settings.
4. If facility is available, the placental should be sent for histopathology in order get extra information.

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Conflicts of interest
There are no conflicts of interest.

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