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Antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre

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Title Page

Antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre

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Short Title: Trisomy 21: 10-year review of antenatal and postnatal findings

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Abstract *(200/200 words)*

Objective

To examine the antenatal imaging features, intrapartum findings and early postpartum course of pregnancies with trisomy 21 (T21) at a tertiary hospital in the UK.

Methods

Women with pregnancies diagnosed with T21 on antenatal or post-mortem/postnatal karyotyping, from February 2010-2020. Outcome measures included antenatal imaging findings, fetal growth restriction (FGR), birthweight, mode of delivery, and early neonatal outcomes.

Results

Seventy-six women were included. There were six intrauterine deaths and 70 livebirths. Thirty-eight (50%) had an antenatal diagnosis and twenty-five (33%) had a suspected diagnosis but declined further testing. The diagnosis was unanticipated in 13 (17%). Cardiac anomalies (35.5%) were the most common antenatal anomaly. Doppler abnormalities were apparent in 48/73 (68%). Eighteen (25.7%) had antenatal FGR. The majority delivered by Caesarean section, and 21.4% of babies weighed <3rd percentile at delivery. Fifty-eight (82%) were admitted to the neonatal unit. Forty-three (61%) required respiratory support and fifty-five (78%) needed naso-gastric feeding or were nil by mouth. Mean PAPP-A values were significantly lower in cases with abnormal Dopplers, FGR, congenital anomalies and birthweight <10th percentile.

Conclusions

T21 fetuses have high rates of placental insufficiency, FGR and Doppler abnormalities. Postnatally, most require respiratory and feeding support. Antenatal counselling should reflect these risks.

Keywords

Trisomy 21

Introduction *(332/400 words)*

Trisomy 21 (T21) is a common aneuploidy with a live birth prevalence in Europe of just over 1:1000. (1) As average maternal age advances and screening improves, due in part to the adoption of non-invasive prenatal testing (NIPT), it is likely that rates of antenatal detection of trisomy (T21) will increase. (2)

Prenatal diagnostic testing for T21 was first carried out in 1966, a century after Langdon Down originally described the phenotype. (3) This prenatal diagnosis was achieved with karyotyping of cells retrieved from fetal amniotic fluid. Diagnostic testing with amniocentesis or chorionic villus sampling (CVS) remains the gold standard for achieving a prenatal diagnosis, but huge changes have impacted screening regimens for T21, which have variously incorporated maternal age, placental biochemistry, ultrasound markers and, most recently, cell-free fetal DNA in an effort to improve screening performance.

Despite this rapid evolution in aneuploidy screening, there remains a paucity of evidence and guidance around the optimum management of pregnancies where T21 is strongly suspected or confirmed and where parents are committed to continuing the pregnancy. Frequency of scanning protocols and guidance on timing of delivery have not been fully elaborated but there is evidence that pregnancies affected by T21 have higher rates of stillbirth, preterm delivery and fetal growth restriction (FGR) compared to euploid fetuses (4, 5). Furthermore, it is well established that the typical placental biochemistry signature associated with T21, such as a suppressed pregnancy-associated plasma protein-A (PAPP-A) is, in euploid pregnancies, associated with adverse obstetric outcomes. (6)

In this study, we sought to improve the evidence and counselling base for those who may be minded to continue with a pregnancy affected by T21, following either antenatal diagnosis or high-chance screening results. Through this 10-year retrospective review, comprising the

largest European case series of pregnancies affected by T21, we sought to consider antenatal imaging findings, fetal well-being in the third trimester by means of Doppler studies, intrapartum events and post-partum outcomes to better understand and manage ongoing pregnancies with T21.

Methods

Study population and design

We included all women with an antenatal or postnatal diagnosis of T21 who had antenatal care at University College Hospital between February 2010-February 2020, and who, if they had a livebirth, delivered at the same hospital.

Data was retrieved from local databases: all consecutive cases of T21 on karyotyping after prenatal diagnostic testing (CVS or amniocentesis), and all high chance NIPT results were included. All cases where parents opted for a termination of pregnancy were excluded. Additionally, all neonatal karyotype samples positive for T21 and post-mortem T21 karyotypes were also included.

Gestational age was calculated either by measurement of the crown-rump length (CRL) or by head circumference if women attended later than scheduled for their booking scan (11+2-14+1 weeks' gestation) and the CRL was in excess of 84mm. At the time of this scan, women were offered screening for aneuploidy, incorporating the fetal nuchal translucency measurement, maternal age and placental biomarkers, measured using the DELFIA XPRESS system (*PerkinElmer Life and Analytical Sciences, Waltham, MA, USA*). PAPP-A measurements were expressed as multiples of the median (MoM), using reference ranges established by the Fetal Medicine Foundation. (7)

Maternal demographics including parity and age were recorded. *Anomalies apparent on ultrasound imaging at any gestation were recorded*. In our centre, all women with an antenatal diagnosis of T21 are invited to attend for specialist fetal echocardiography, and these results were recorded.

Third trimester scan findings were also considered. Women with an antenatal diagnosis of T21 are offered routine ultrasound at 28, 32 and 36 weeks of gestation and scans may be carried out more frequently if there are additional concerns. Estimated fetal weight (EFW) was derived using the Hadlock formula (8). This method has been shown to be more accurate than other approaches. (9) To assess placental function, Doppler evaluation of the umbilical artery (UA) and middle cerebral artery (MCA) was carried out in the third trimester. Doppler studies were considered abnormal if the UA pulsatility index (PI) was above the 95th percentile, or if there was absent or reversed end diastolic flow, or if the MCA-PI was below the 5th percentile, or if the cerebroplacental ratio (CPR) was below the 5th percentile. Reference ranges established by the Fetal Medicine Foundation, in a study of over 70,000 patients, were used. (10)

Additionally, we considered the presence of FGR according to the consensus definitions established by ISUOG – *International Society of Ultrasound in Obstetrics and Gynaecology*. (11). In keeping with this definition, fetuses were described as having early FGR if, on ultrasound examination prior to 32 weeks' gestation, they had an EFW or AC <3rd percentile, or if they had an AC/EFW <10th centile with either a uterine or UA-PI >95th percentile.

Fetuses were described as having late FGR after 32 weeks' gestation if they had an EFW or AC <3rd percentile or at least two out of three of: AC/EFW <10th percentile; AC/EFW crossing centiles >2 quartiles on growth centiles; CPR <5th percentile or UA-PI >95th centile

Intrapartum and neonatal outcome data

Gestational age at delivery, the indication for delivery, and mode of delivery were recorded. If delivery was by emergency Caesarean section, the indication for this was recorded.

Neonatal and fetal birthweight centiles were calculated according to the method described by Royston *et al.* (12) and based on locally-derived reference ranges. (13)

Neonatal outcomes were recorded including admission and length of stay to the neonatal unit. If the infant had a postnatal echocardiogram, this was compared to the antenatal findings. Respiratory outcomes including the need for respiratory support (ranging from intubation to the need for facial oxygen) and the presence or absence of pulmonary hypertension were recorded. The need for naso-gastric tube feeding or if the neonate was kept nil by mouth were recorded. Haematological outcomes, including polycythaemia requiring an exchange transfusion, jaundice requiring phototherapy, thrombocytopenia or an early neonatal diagnosis of transient abnormal myelopoiesis (TAM) were also recorded.

Statistical analysis

The Shapiro Wilk test was used to confirm the normal distribution of PAPP-A values prior to analysis. Nuchal translucency values were logarithmically transformed to confer normality. Statistical analysis and comparison of means between groups using the Independent samples t-test was performed using SPSS Version 27 (*IBM Corp., Armonk NY, USA*).

Funding

None

Patient Involvement

No patients were involved in this review

Results

Seventy-six pregnancies were identified. Seventy-five of these cases were singleton pregnancies, one was a dichorionic-diamniotic twin pregnancy.

Maternal Characteristics

The median maternal age was 37 years-old (range 20-50 years-old). Forty (53%) were nulliparous, 36 (47%) were multiparous. Parity ranged from 0 to 14. *The mean BMI was 29.6 kg/m^2 (range 18-46 kg/m^2).*

We considered risk factors for placental insufficiency: one woman had anti-phospholipid syndrome, one woman had chronic hypertension, four (5.2%) developed pre-eclampsia, two (2.6%) had pre-pregnancy diabetes. Four women (5.2%) had thyroid disease (three had hypothyroidism, one had hyperthyroidism). Four women (5.2%) were smokers.

Screening

Fifty-two women had the combined screening test (CST). Of these, 35 had a 'high chance' combined test (defined as a chance of T21 >1:150), and 17 had a low chance CST. Twelve women declined screening, eight women attended at too advanced a gestation to be eligible for the CST, and the results of the CST were unknown in four patients who transferred to UCLH having previously attended other centres (Table 1).

Of those who had the CST, the median nuchal translucency measurement was 2.5mm (range: 1.3-9.2mm). The median PAPP-A was 0.65 MoM (range: 0.06-1.58MoM)

Diagnosis

Confirmation of T21 was achieved antenatally with diagnostic testing (amniocentesis or CVS) in 27 patients. NIPT returned a high-chance result in 11 patients, who did not wish to have diagnostic testing. Given the extremely high sensitivity and specificity of NIPT in a high-risk population (in those with a high chance screen or ultrasound markers of T21) (14) we have considered a high chance NIPT as analogous to a confirmed diagnosis, and during their antenatal course these pregnancies were managed as such. Each of these cases had post-natal genetic testing confirming T21.

The diagnosis was suspected antenatally owing to fetal anomalies in keeping with T21, but unconfirmed as the patients declined further diagnostic testing, in 19 cases (Table 2). The diagnosis was suspected antenatally owing to a high chance CST, but unconfirmed as the patients declined further testing, in six cases. The diagnosis was unanticipated and made postnatally in 13 cases. These cases are described in supplemental table S1.

Of these 13 unanticipated cases of T21, nine had low risk screening tests (table S1). The remaining four either declined or attended too late for screening. Four of the 13 cases where T21 was unanticipated had some concerns on ultrasound, specifically either around fetal size or abnormal Doppler studies or amniotic fluid levels, but no specific offer of diagnostic testing was recorded in the antenatal notes.

Antenatal imaging, (excluding NT)

Out of the 76 cases, 25 (32.9%) had no structural anomalies apparent on ultrasound examination at any point in their pregnancy. Nineteen (25%) had multiple structural anomalies detected at antenatal imaging. Structural anomalies detected antenatally, organised by system are displayed in figure 1A.

Cardiac anomalies (n=30) were the most common structural anomaly detected antenatally. Septal defects were the most common type of structural congenital cardiac abnormality. Types of cardiac anomaly are presented in figure 1B.

Among the cases where a gastrointestinal anomaly was noted, duodenal atresia was suspected in five cases, an echogenic-appearing bowel was noted in four cases (but was found in association with other anomalies in each case), and hepatomegaly noted in three cases.

The most common renal anomaly was renal pelvis dilatation, noted in seven cases, but was found in associated with other anomalies in each case. Ventriculomegaly was noted in seven cases, and was the most common neurological structural anomaly.

Pleural effusions were noted in four cases and was the most common respiratory / thoracic anomaly.

Mean NT measurements were greater in cases with anomalies (mean NT=3.38mm) compared to those with no anomalies (mean NT=2.78mm). Using the Independent samples T-test, there was a significant difference ($p \leq 0.001$) observed in the NT measurement between those with antenatal anomalies detected on ultrasound, and those with no anomalies detected, where the NT was smaller. There was also a significant difference ($p \leq 0.001$) in the PAPP-A MoM between those cases with a fetal anomaly, characterised by a reduced PAPP-A, and those with no anomaly, with a PAPP-A that was closer to normal. (Table 3)

Third trimester fetal well-being scans

Seventy-three out of the cohort of 76 patients had 3rd trimester ultrasound scans. Of these, 48

(65.8%) had abnormal Doppler studies at their final scan in the third (defined as either an UA-PI >95th percentile, or an MCA-PI <5th percentile, or a CPR <5th percentile).

We recorded the gestational age the Doppler studies first became abnormal, which may have been either at their final scan or preceding this. The median time from the first appearance of abnormal Dopplers in the third trimester and delivery was 10 days.

The median EFW percentile at the final third trimester ultrasound prior to delivery was 23.6. Twenty-five (34.2%) cases had an EFW less than the 10th percentile at the final third trimester ultrasound. There was a significant difference between the PAPP-A MoM in those cases with abnormal Doppler studies in the third trimester, compared to those who had normal Dopplers (Table 3).

Eighteen (25.7%) of the cohort of 73 who had 3rd trimester ultrasounds had FGR according to the ISUOG consensus definition. Thirteen were classified as having early growth restriction, five as late. The mean PAPP-A MoM was significantly lower ($p \leq 0.001$) in the group that had growth restriction compared to those that did not.

In the third trimester, five (15%) cases were recorded as having polyhydramnios (amniotic fluid index or deepest vertical pool >95th centile) on ultrasound examination. Two of these cases of polyhydramnios were seen in conjunction with scan findings in keeping with duodenal atresia. One woman had amniodrainage for maternal symptoms. Oligohydramnios was recorded in two cases (2.6%), in one case, in conjunction with abnormal Doppler studies (CPR <5th percentile) and the other was an isolated finding.

Intrapartum findings

Seventy (92.1%) women had a live birth and six (7.9%) had an *in-utero* death (IUD). Details

of these IUDs are presented in supplemental table S2. *For comparison, rates of IUD (after 24 weeks' gestation) in our unit were <1% (2020-2021).*

Of the 70 women who had a live birth of a baby with T21, 41 (58.6%) were delivered by Caesarean section. Thirty women had an emergency (39.5%), and 11 (15.7%) had an elective Caesarean section.

Of the 30 women who had an emergency Caesarean section, 21 were delivered either because of fetal concerns on cardiotocography monitoring or escalating concerns around fetal well-being from ultrasound Doppler studies. Of those who had an emergency Caesarean section, 11 were delivered without labouring, either because an induction was considered inappropriate owing to the gestation, concerns around Doppler studies, or malpresentation.

Twenty-nine (41.4%) women had a vaginal delivery. Of these, three were delivered with a ventouse suction cup and two by forceps.

The median gestational age at delivery was 37.9 weeks, (range 28weeks+3 days – 41weeks+6 days). Of the 70 women who had a live birth of a baby with T21, 24 (34.3%) delivered preterm (<37 weeks' gestation). Nineteen had an iatrogenic preterm delivery, 13/19 (68.4%) were indicated because of concerns around fetal well-being at third trimester ultrasound. Five women (7.1%) had a spontaneous preterm delivery (range 28+3 days – 37 weeks' gestation) . Data on preterm delivery is presented in supplemental table S3.

Birthweight & Neonatal outcomes

Birthweights of the 70 live-born babies with T21 ranged from 810g to 4383g. The median

birthweight percentile was 18.9. Fifteen (21.4%) babies were born <3rd percentile, 17 (24.3%) were <5th centile, and 25 (35.7%) were <10th centile.

Using the two-tailed T-test, a significant difference ($p \leq 0.001$) was observed in PAPP-A MoM between those with a birthweight above the 10th percentile and those with a birthweight below the 10th percentile, indicating that the correlation between birthweight and suppressed PAPP-A persists in the context of T21, as well as in euploid fetuses. This data are displayed in Table 3.

Fifty-eight (82%) were admitted for care to the neonatal unit, and the median length of stay at the unit was 10 days. Thirty-six infants were transferred to another unit after their neonatal admission, (including for surgical or critical cardiac care at a tertiary centre). Twenty-two were discharged home. There were no neonatal deaths during the early post-natal stay. Forty-three (61%) required respiratory support at some point during their stay and eight (11%) had pulmonary hypertension.

A high proportion of babies required feeding support: 44 (65%) needed support with tube feeding, 11 (16%) were kept nil by mouth. Four babies had duodenal atresia confirmed postnatally which was suspected antenatally in each case.

Thirty-four (52%) of babies had jaundice requiring phototherapy. Ten (15%) had polycythaemia requiring an exchange transfusion. Thrombocytopenia was diagnosed antenatally in 19 (29%) infants. Transient abnormal myelopoiesis (TAM) was diagnosed postnatally in 6 cases.

Discussion

Main Findings

There are high rates of Doppler abnormalities, FGR, and birthweights <3rd percentile in pregnancies with T21. Low levels of PAPP-A correlate with a more severe phenotype with higher rates of congenital anomalies, FGR and abnormal Dopplers.

Strengths and Limitations

This study combines antenatal imaging, biochemical markers of placental function, intrapartum events and early post-natal outcomes in a large case series of fetuses/neonates with T21. By correlating Doppler studies, FGR and birthweight indices to PAPP-A values we have shown there is likely to be a pathological placental process underlying the high rates of abnormal Doppler findings in pregnancies affected by T21, and we have shown that low levels of PAPP-A reflect a higher risk of fetal anomaly and a higher risk of placental insufficiency, as is already well described in euploid fetuses. We have expanded the evidence to allow for comprehensive and timely counselling of parents at the time of antenatal diagnosis around the anticipated neonatal course for their baby. We have included antenatal, post-natal or post-mortem diagnoses of T21 in order to more accurately reflect the risk of IUD with T21, and also to allow for a more comprehensive account of the neonatal course. Cases with an antenatal diagnosis may have a more severe phenotype, prompting the prenatal diagnosis, and so exclusively examining this cohort may not be representative of all diagnoses.

Study limitations include that we have not considered longer term neonatal outcomes, and a proportion of babies were transferred to other units for treatment. We did not have access to these outcomes following transfer. Additionally, we may have missed some postnatal

diagnoses of T21 following neonatal discharge. It is unlikely this will have occurred frequently as T21 is usually a readily recognisable phenotype. We acknowledge the ISUOG consensus definition for FGR applies to fetuses without congenital anomalies. By combining EFW, Doppler indices, and decrements in growth velocity, this definition does seek to reflect true placental pathology rather than constitutional phenotype. Using EFW as the sole marker for placental performance would be inappropriate in this cohort since it is well established that the T21 phenotype is associated with reduced weight at delivery and early neonatal period. (15)

Interpretation

High rates of abnormal Doppler studies in the third trimester have been observed previously (5, 16). Wagner *et al.* reported an UA-PI mean z-value of 2.20 at 35 weeks' gestation, but this did not correlate with a reduced abdominal circumference. They concluded that the raised UA-PI did not reflect true placental pathology. (16) Corry *et al.* (17) have also shown T21 pregnancies have higher UA-PIs than euploid pregnancies and considered these pregnancies were more likely to have placental insufficiency as evidenced by signs of maternal vascular malperfusion on histopathological examination of the placenta. The authors suggested the pathological haematological profile associated with T21 may explain placental pathology, and the polycythaemia found in T21 may cause thrombi and placental infarction.

PAPP-A measured between 10-14-weeks' gestation, has been shown in euploid pregnancies to be inversely associated with a higher risk of adverse obstetric outcomes, including FGR and gestational hypertension. (6, 18). A significant association between low PAPP-A and congenital heart disease (CHD), independent of aneuploidy, has also been demonstrated previously and it has been postulated that reduced perfusion of the placenta and associated

fetal hypoxia could induce congenital defects. (19) An association between placental dysfunction and congenital cardiac anomalies has also been demonstrated on histopathological placental examination in CHD. (20)

Our study, demonstrating that a low PAPP-A level was significantly associated with a birthweight <10th percentile, FGR and abnormal Dopplers, lends weight to the hypothesis that these findings are associated with placental pathology, rather than simply being a benign finding in T21.

Because of the correlation between low PAPP-A levels and higher rates of placental dysfunction and structural anomalies in T21, we would suggest detailed and frequent ultrasound examination in this cohort.

To provide more context for the high rates of low birthweight in the T21 cohort we considered birthweight centiles in our institution over two years, (2020-2021). In 2020, 549 (9.93%) babies were < 10th percentile at delivery. In 2021, 521 babies (9.94%) were <10th percentile at delivery.

The background maternal obstetric risk factors for placental insufficiency, which we have described above, are broadly in keeping with what one would expect among an older-than average maternal cohort and do not in themselves account for the high levels of observed placental dysfunction in this cohort.

Higher rates of placental pathology are also reflected in the high rates of delivery by Caesarean section. The most common indications for surgery were in keeping with suboptimal placental function, such as concerns on cardiotocography monitoring. High rates of Caesarean section in T21 pregnancies have been reported in previous studies. (4)

Placental pathology may also be implicated in the higher rates of IUD observed in fetuses with T21, compared to euploid fetuses (5). The cases in our cohort that occurred after 20 weeks were preceded by abnormal Dopplers and FGR. Our finding of an IUD rate of 7.9% is in keeping with a large registry of T21. (21)

For comparison and to provide context for the high rates of IUD in fetuses with T21, we considered rates of stillbirth after 24 weeks in our unit over 2 years (2020-2021): In 2020 there were 18 stillbirths from a total of 5,526 deliveries (0.33%). In 2021 there were 34 stillbirths from a total of 5242 deliveries (0.65%).

The risks of IUD escalate sharply after 38 weeks' gestation, from a background risk significantly higher compared to term euploid fetuses. (22)

Previously, histopathological characteristics underlying placental dysfunction in pregnancies complicated by trisomy 21 have been explored: placentas in T21 pregnancies have been shown to be prematurely senescent compared to placentas from euploid pregnancies. (23) Accelerated telomere shortening, considered a biomarker for aging, has also been observed in amniocytes in T21 pregnancies. (24) Changes analogous to those seen in pre-eclampsia have also been observed in T21 placentas, with abnormal fibrinoid deposition, defects in cytotrophoblast differentiation, and lower levels of PLGF expression. (25, 26)

Our work illustrates the need for close surveillance during the third trimester to interrogate growth velocity and Doppler changes. It is noteworthy that the average duration from the first finding of abnormal Dopplers to delivery was just 10 days. Given the prevalence of Doppler changes, and the evidence around timing of delivery in T21 from previous work, we support a policy of offering delivery by 38 weeks' gestation.

T21 was confirmed or suspected in 82.9% of our cohort. A significant proportion of our cohort declined diagnostic testing, and 11 declined diagnostic testing to confirm a high-chance NIPT result. Given this cohort examines findings in ongoing pregnancies with T21, rather than those who opted for termination, it is unsurprising that many mothers would not want to undergo a procedure with a small miscarriage risk. (27)

Sixty-seven percent of our cohort had one or more congenital anomalies identified on ultrasound, a slightly lower rate than that found by Guseh *et al.* (5). This study however, only considered cases where there was an antenatal diagnosis of T21, and those cases with no abnormalities apparent on ultrasound may be less likely to be diagnosed *in-utero*.

Cardiac abnormalities were the most frequently found congenital anomaly *and septal defects were the most common type of cardiac anomaly*, (4) which is in keeping with the distribution of structural cardiac pathology in children with T21. (28) Recent studies have shown the prognosis for infants with T21 who undergo surgery for septal defects is excellent, and parents should be counselled appropriately when such lesions are found antenatally. (29) (30)

Postnatally, there is a high chance of admission to the neonatal unit, which should be discussed antenatally. We have shown there are high rates of babies with T21 requiring both ventilatory support and tube feeding. Similarly high rates of feeding support have been shown in previous studies. (31) Prematurity, low birth weight, hypotonia, and structural defects may be contributory factors in feeding difficulties. (31)

Feeding difficulties may induce strong feelings of stress and anxiety and parents should be counselled around the high chance of their baby requiring help with feeding, and emotional and practical support should be available. (31)

High rates of jaundice requiring therapy were found in our cohort, a phenomenon well described in T21, and which is thought to relate to decreased bilirubin elimination and abnormal erythropoiesis. (32) Parents should be counselled about the likelihood of their baby needing treatment for jaundice and the 10% risk of requiring exchange transfusion.

In summary, this study provides evidence for close ultrasound surveillance of pregnancies where trisomy 21 is highly suspected or diagnosed. We would suggest at least fortnightly ultrasound scans in the third trimester to interrogate for placental function and fetal well-being. Changes that can be associated with TAM, such as hepatomegaly may also be seen in the third trimester, and antenatal suspicion of this may facilitate timely postnatal management.

Future research directions should include further analysis of placental histopathological changes associated with trisomy 21, and clinical consideration of the efficacy of aspirin to improve placental performance in trisomy 21 even in the absence of other risk factors for growth restriction and pre-eclampsia.

Conclusion

We have shown pregnancies with T21 have a high risk of placental insufficiency, with high rates of low birthweight for gestation/FGR and high rates of abnormal Doppler studies. Each of these abnormal findings correlate with a significantly lower PAPP-A.

Pregnancies with T21 are likely to require delivery by emergency Caesarean section and, in the post-partum period, there is a high chance of the neonate requiring admission to the neonatal unit for feeding and respiratory support and treatment for jaundice.

This study will aid counselling of parents who are either considering or committed to continuing with a pregnancy where T21 is diagnosed or suspected. We have shown close Dopplers surveillance in the third trimester should be recommended and our study strengthens the evidence base for offering delivery by 38 weeks.

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Disclosure of Interests

No other authors report any conflict of interest

Contribution of Authorship

DS conceived the idea. FDS, DS, AR and EH collected all the data. FDS, DS and PPP analysed the data. DS prepared the first draft of the manuscript. All authors reviewed and significantly contributed to the final version of the manuscript.

Details of Ethical Approval

This review was performed as part of a service evaluation and therefore ethical approval was not required.

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Table 1 – Results of the combined screening test (CST) of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre.

CST	**n (%)**
High chance	35 (46.1)
Low chance	17 (22.3)
Declined	12 (15.8)
Late booker (ineligible)	8 (10.5)
Unknown	4 (5.3)

Table 2 – Diagnosis of T21 made on the basis of diagnostic/non-diagnostic testing or on the basis of findings from antenatal ultrasound/screening results of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre. CVS – chorionic villous sampling; NIPT – non-invasive prenatal testing

	n (%)
Antenatal Diagnosis	**38 (50%)**
Amniocentesis / CVS	27 (35.5%)
NIPT alone	11 (14.5%)
Diagnosis suspected	**25 (32.9%)**
Fetal anomaly	19 (25%)
High chance screening	6 (7.9%)
Diagnosis unanticipated antenatally and made postnatally	**13 (17.1%)**

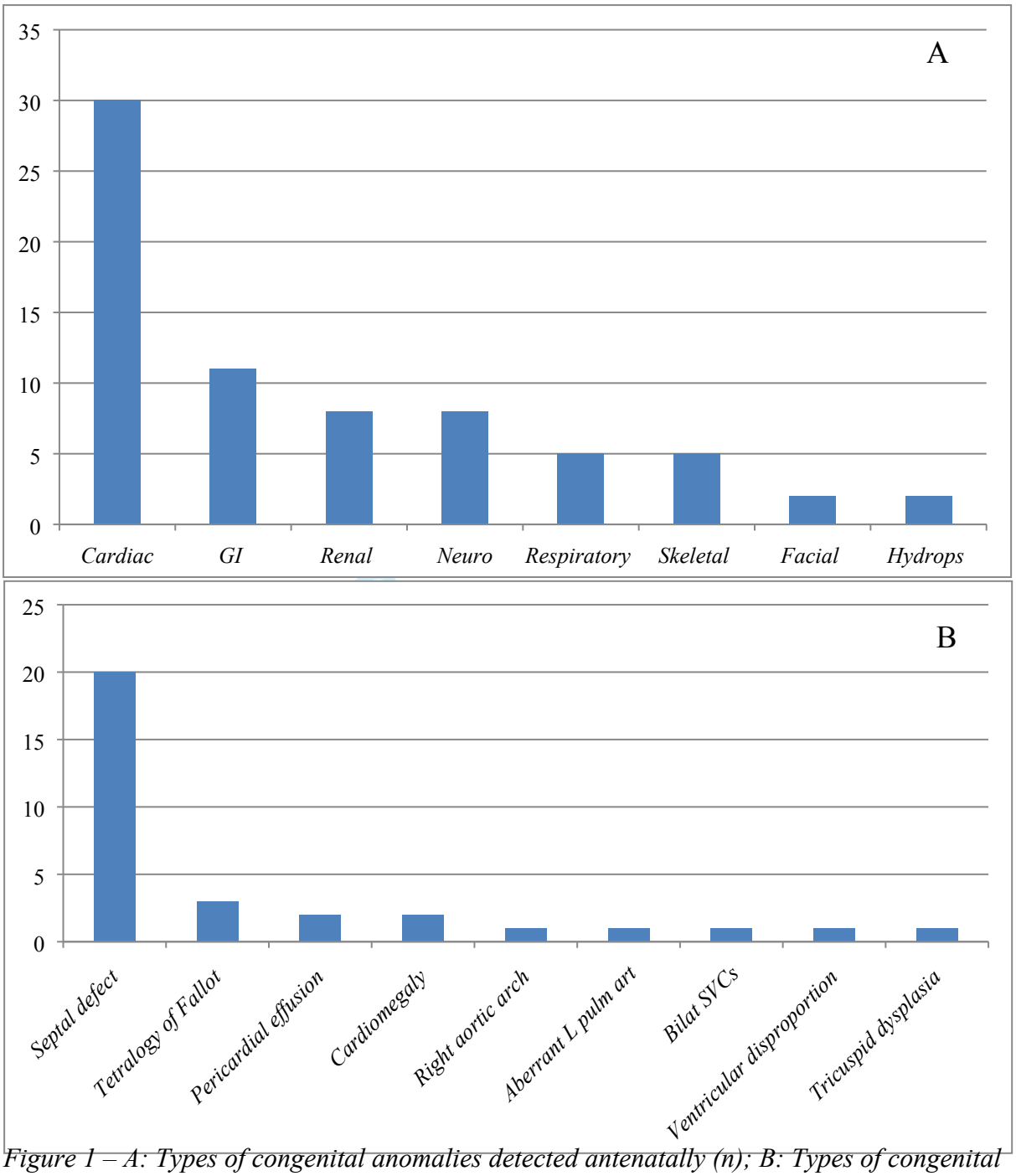

Figure 1 – A: Types of congenital anomalies detected antenatally (n); B: Types of congenital cardiac anomaly detected antenatally.

Table 3 – Mean values of nuchal translucency (NT, mm) and PAPP-A (pregnancy associated plasma protein-A, MoM – multiples of the median) for cases with and without fetal anomaly

detected by ultrasound antenatally and association of mean PAPP-A levels and birthweight percentile, presence of fetal growth restriction (FGR) and Doppler studies. Significance level: p<0.05. SD – standard deviation; SE – standard error.

Mean values of nuchal translucency (NT, mm) measurements and PAPP-A (pregnancy associated plasma protein-A, MoM – multiples of the median) levels for cases with and without fetal anomaly detected by ultrasound antenatally. FGR – fetal growth restriction; ISUOG – International Society of Ultrasound in Obstetrics and Gynaecology; SD – standard deviation; SE – standard error.

	Mean	**SD**	**SE**	**p value**
LogNT: anomaly	0.46 mm	0.23	0.05	<0.001
LogNT: no anomaly	0.40 mm	0.19	0.04	
PAPP-A: anomaly	0.53 MoM	0.37	0.09	<0.001
PAPP-A: no anomaly	0.72 MoM	0.35	0.08	

Association of mean PAPP-A (pregnancy associated plasma protein-A, MoM – multiples of the median) levels and birthweight percentile, presence of fetal growth restriction (FGR) and Doppler studies.

	PAPP-A	**SD**	**SE**	**p value**
Birthweight <10th percentile	0.47	0.3328	0.096	<0.001
Birthweight >10th percentile	0.77	0.3728	0.085	<0.001
FGR *(ISUOG)*	0.49	0.3003	0.070	<0.001
No FGR *(ISUOG)*	0.76	0.3389	0.088	<0.001
Abnormal Doppler studies	0.57	0.369	0.081	<0.001
Normal Doppler studies	0.79	0.396	0.125	<0.001

Table 1 – Results of the combined screening test (CST) of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre.

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Table 2 – Diagnosis of T21 made on the basis of invasive/non-invasive testing or on the basis of findings from antenatal ultrasound/screening results of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre. CVS – chorionic villous sampling; NIPT – non-invasive prenatal testing

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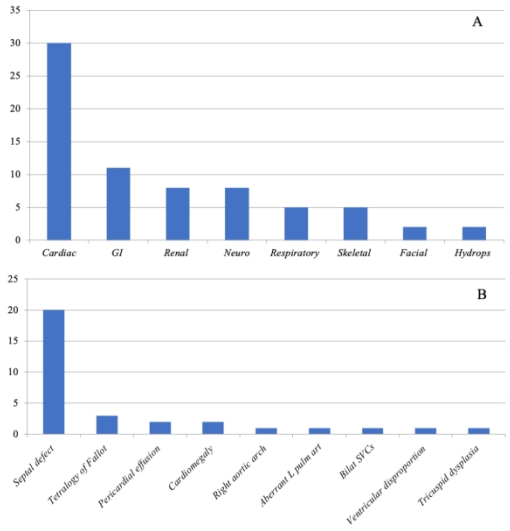

Figure 1 – A: Types of congenital anomalies detected antenatally (n); B: Types of congenital cardiac anomaly detected antenatally

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Supplemental table S1 *– Details of the cases with unanticipated postnatal diagnosis of T21 of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre.*

CST – Combined screening test; DCDA – dichorionic diamniotic; IOL – induction of labour; IUGR – intrauterine growth restriction; USS – ultrasound; PPROM – preterm prelabour rupture of membranes; SGA – small-for-gestational age; TAM – transient abnormal myelopoiesis; VSD – ventricular septal defect.

Case	***Screening***	***Ultrasound findings***	***Intrapartum events/ post-partum anomalies***	***Gestation at delivery, birthweight (centile)***
1	Low risk CST	DCDA twin, normal USS	Spontaneous preterm labour 35+5	35+6, 3400g, (98.7)
2	Low risk CST	Normal USS	PPROM, IOL at 36/40 VSD diagnosed postnatally	36, 3020g (82.6)
3	Low risk CST	IUGR suspected on 3rd trimester scan.	TAM diagnosed postnatally	37+6 2840g (26.9)
4	Low risk CST	SGA & abnormal Dopplers at 3rd trimester USS	IOL due to SGA	39+6, 2850 (7.8)
5	Low risk CST	Normal USS	Spontaneous term delivery	40+4, 3992g (85.6)
6	Low risk CST	Normal USS	Small VSD diagnosed postnatally	40+0, 2570g (1.6)
7	Low risk CST	Normal USS	Spontaneous term delivery	41+2, 3539g (40.7)
8	Low risk CST	Normal USS	TAM diagnosed postnatally	41+6, 3015g (5.5)
9	Late booker, low risk Quad test	Normal USS	Spontaneous term delivery	39+0, 3020g (25.0)
10	Declined CST	Normal USS	VSD diagnosed postnatally	38+5, 3030g (29.9)
11	Late transfer of care, missed CST	IUGR on 3rd trimester USS	IOL owing to IUGR	38+5 2470 (2.7)
12	Declined CST	Normal USS	Spontaneous term delivery	38+6, 3840g (92.3)
13	Late booker, declined Quad test	Anhydramnios and abnormal Dopplers at 3rd trimester USS	IOL due to anhydramnios / abnormal Dopplers	39+3, 2830g (9.5)

Supplemental table S2 *– Cases of intrauterine death (IUD) of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre.*

CPR – cerebro-placental ratio; CST – Combined screening test; CVS – chorionic villous sampling; EDF – end-diastolic flow; EFW – estimated fetal weight; UA – umbilical artery; VSD – ventricular septal defect.

Gestation at IUD	Anomalies detected antenatally	Antenatal diagnosis
36+1	Right aortic arch, VSD. EFW <10th percentile and CPR <5th percentile	Confirmed (amniocentesis)
34+6	VSD, duodenal atresia. EFW <10th centile and intermittent absent EDF in UA	Confirmed (amniocentesis)
33+4	Tetralogy of Fallot, bilateral ventriculomegaly. EFW <10th percentile & reversed EDF in UA	Suspected: High risk CST, declined further testing. Confirmed at post-mortem
19	Renal pelvis dilatation	Confirmed (amniocentesis)
15+5	Hydrops	Confirmed (CVS)
15	Nil noted	Confirmed (CVS)

Supplemental table S3 *– Cases preterm delivery and respective indication of women included in the review of antenatal findings and early postnatal outcomes in pregnancies with trisomy 21: a 10-year retrospective review at a tertiary centre.*

APH – antepartum haemorrhage; IUD – intrauterine death; PET – preeclampsia; PPROM – preterm prelabour rupture of membranes.

Timing and indication for delivery	***n (%)***
Delivery prior to 37 weeks' gestation	24 (37.1)
Delivery after 37 weeks' gestation	46 (62.9)
Iatrogenic delivery prior to 37 weeks' gestation	19 (27.1)
- *Abnormal Dopplers*	13
- *Maternal PET*	1
- *PPROM*	2
- *Hydrops*	1
- *Maternal Hx (previous IUD)*	1
- *APH*	1
Spontaneous Preterm Delivery	5 (7.1%)