Comment on: The assessment of combined first trimester screening in women of advanced maternal age in an Asian cohort

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Dear Sir,

We read with great interest the article by Li et al,[1] as we were keen to see if the performance of first trimester screening (FTS) at their tertiary maternity centres (i.e. National University Hospital and Singapore General Hospital) was similar to that at KK Women's and Children's Hospital (KKH).[2] At KKH, with a risk cut-off value of 1:300, the sensitivity of FTS was 81.8% with a false positive rate (FPR) of 5.4% (without nasal bone incorporated), and 90.9% with an FPR of 3.7% (with nasal bone incorporated). Compared to those in Li et al's study, the mothers at KKH were, on average, younger (18.7% aged ≥ 35 years, median age 31 years). Furthermore, in their study, when the risk cut-off values of 1:250 and 1:300 were applied, the detection rate of FTS for trisomy 21 (T21) was 86.5% with an FPR of 2.38% and 2.77%, respectively. The screening efficiency of the different institutions would be similar if the same FPRs were used for comparison.

The prevalence of T21 in Li et al's study was 3.6 per 1,000 cases, i.e. 1:278. This is much higher than that generally quoted (1:500–1,000), even after accounting for the 30%–50% miscarriage rate between 12 weeks and term. Furthermore, the ratio of T21:T18:T13 in their study was 37:11:1, while the data from the National Birth Defects Registry of Singapore from 1994 to 2000 gives a ratio of 8.2:2.9:1. These suggest that Li et al's study cohort was selected from a population of mothers at high risk. This is also evidenced by the higher proportion of older mothers in their study compared to the hospital's delivery population (26.1% vs. 14.9%; Table VI[1]). This factor is of utmost importance, as the figures derived from such a study cohort cannot be used in counselling for the general low-risk population.

It is surprising that Li et al did not find a significant difference in the performance of FTS when they dichotomised the study population into groups of age < 35 years and ≥ 35 years. As the algorithm uses maternal age as the *a priori* risk, and this risk increases with advancing maternal age, we expected an increased detection rate (sensitivity) among the older mothers, with an increased screen-positive rate at any given fixed risk cut-off value; analysis of maternal age by five-year intervals might be able to confirm this. One possible explanation could be that a group of high-risk mothers who were found to have an increased nuchal translucency opted for an invasive procedure without having the serum screening component done, therefore contributing to the decrease in the numerator of detection rate in the age ≥ 35 years group. The other possibility is the under-ascertainment of screen-negative older mothers who chose to deliver outside of the institutions (quoted as 50%[1]). We are confused by the claim that "all delivery outcomes in the screen-negative group were known" as "there is no established computerised system" (presumably a purpose-designed database) to capture this information. Mothers who deliver outside of the institution are unlikely to have their babies' karyotypes sent to institutional cytogenetic laboratories. One way to reduce under-ascertainment would be to seek the help of the National Birth Defects Registry to cross-reference the databases. Another method would be to model the expected number of T21, T18 and T13 cases from the maternal age distribution using known age-related risk algorithms.

We would like to emphasise that ultrasonography done at 12 weeks also screens for structural anomalies, which account for the majority of congenital birth defects (e.g. anencephaly) and are largely independent of chromosomal abnormalities such as Down syndrome, which contributes to only about 10% of birth defects. We also wish to highlight that there is a typographical error in Fig. 1 – the number of T21 should be 31 and not 3.

In conclusion, Li et al's findings strongly suggest that their study cohort was selected from a high-risk patient population (very likely due to referral and selection bias) and thus, the figures derived cannot be generalised to the low-risk patient population. However, we would like to congratulate the authors for using the data to audit their clinical performance and standards of practice.

Yours sincerely,

Fon-Min Lai[1], George SH Yeo[1]

[1]Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore. dr.george.sh.yeo@gmail.com

References

1. Li SW, Barrett AN, Gole L, et al. The assessment of combined first trimester screening in women of advanced maternal age in an Asian cohort. Singapore Med J 2015; 56:47-52.
2. Yeo GS, Lai FM, Wei X, et al. Validation of first trimester screening for trisomy 21 in Singapore with reference to performance of nasal bone. Fetal Diagn Ther 2012; 32:166-70.