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Trends in resource use for, and effectiveness of, prenatal diagnosis of birth defects by ultrasound in France: Are we getting our money's worth?

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Abstract

Objective: To analyze trends in the number of ultrasound examinations in relation to the effectiveness of prenatal detection of birth defects using population-based data in France.

Design: A multiple registry-based study of time trends in resource use (number of ultrasounds) and effectiveness (proportion of cases prenatally diagnosed)

Setting: France. Three registries of congenital anomalies (effectiveness) and data on ultrasounds for all pregnant women.

Participants: Two samples of pregnant women. The effectiveness was assessed using data from three French birth defect registries. Resource use for the ultrasound screening was based on the French national healthcare database.

Main outcome measures: Prenatal diagnosis (effectiveness) and average number of ultrasounds (resource use). Statistical analyses included linear and logistic regression models to assess trends in resource use and effectiveness of prenatal testing, respectively.

Results: The average number of ultrasounds per pregnancy significantly increased over the study period, from 2.47 in 2006 to 2.98 in 2014 (p=0.005). However, there was no significant increase in the odds of prenatal diagnosis. The probability of prenatal diagnosis was substantially higher for cases associated with a chromosomal anomaly (91.2%) than those without (51.8%). However, there was no evidence of an increase in prenatal detection of either over time.

Conclusions: The average number of ultrasounds per pregnancy increased over time whereas the probability of prenatal diagnosis of congenital anomalies did not. Hence, there

is a need to implement policies, in particular more high-quality training programs, which can improve the efficacy of US examinations for prenatal diagnosis of congenital anomalies.

Keywords: Birth defect; Ultrasound; Effectiveness; Prenatal diagnosis.

Article summary, strengths and limitations of this study:

- We observed the evolution of the French ultrasound birth defect screening program's effectiveness, between 2006 and 2014.
- We measured the birth defect detection rate and the number of screening ultrasound per pregnancy to assess the efficacy of and the resources used by the program.
- We used two large data sources: national registries of birth defect and the national claims database.
- We excluded from the calculation prenatal ultrasound unrelated with the screening and birth defects prenatally diagnose by other modalities than ultrasound.
- There wasn't an exact correspondence between the population of the two data sources.

Introduction

Congenital abnormalities occur in approximately 2 percent of all live births[1]. They comprise one of the leading causes of infant mortality and morbidity in industrialized countries[2–4]. Prenatal diagnosis of congenital abnormalities is a prerequisite for adequate prenatal counseling and management. In particular, in case of severe, incurable abnormalities, it offers to the parents the possibility of Termination of Pregnancy for Fetal Abnormality (TOPFA).

In France, the prenatal screening for fetal anomalies is organized by laws and recommendations. Three ultrasound (US) screening examinations are recommended in singleton pregnancies at 11-14 weeks', 20-25 weeks' and 30-35 weeks' gestation (WG)[5]. Besides this ultrasound screening, a first trimester combined test is offered to each pregnant woman for the evaluation of risk for Down's syndrome[6]. When a fetal anomaly is suspected, the patients are referred to specialized referral centers to perform further investigations[7]. There are 49 referral centers for prenatal diagnosis in France and its territories. When a severe fetal anomaly is confirmed, TOFPA is authorized up to the end of the pregnancy, at the request of the mother, once two experts have certified the severity of the fetal anomaly[8].

The French national health insurance covers the entire cost of the prenatal screening of fetal anomalies. However, the number of ultrasounds performed per pregnancy and its result in terms of prenatal detection rate for fetal anomalies have never, to our knowledge been studying so far, while representing a significant amount of public ressources. Same goes for other countries too, as of today. This data could be of interest to both the care

providers as well as the governments in order to allocate better the fund which can be used more effectively.

Our objective was to assess the effectiveness of ultrasound prenatal screening for fetal anomalies by measuring the evolution of the resources used and the proportion of cases that were prenatally diagnosed between 2006 and 2014, in France.

Data and methods

Data sources, Patients and Public involvment

We used two data sources for our study. In order to look at trends in the average number of ultrasounds per pregnancy, we used specific data from the national claims database: the Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM)[9]. Our data source was the *Echantillon Généraliste des Bénéficiaires* (EGB), a permanent representative sample of 1/97 of the individuals covered by the French Health Insurance System[10]. It was a time-trend observation on aggregated data, provided by an analysis on anonymised individual data, and didn't require ethical approve. The EGB analysis, part of the SNIIRAM and property of the CNAMTS, was performed after INSERM approval and is covered by the *Commission Nationale de l'Informatique et des Libertés (CNIL*) (accords CNIL AT/CPZ/SVT/JB/DP/CR05222O du 14/06/2005 et DP/CR071761 du 28/08/2007). The claims database is exhaustive and covers the entire French population. Each episode of care provided is identified by a code. Multiple codes are used to identify US examinations performed during the pregnancy, depending on the indication: codes differentiate procedures related to the detection of fetal anomalies (systematic 1st, 2nd and 3rd trimester

US examinations, US examinations for the monitoring of a known fetal anomaly, fetal echocardiography). Examinations with no relation with the prenatal detection of fetal anomalies (dating US examinations before 11 WG, US examinations for fetal growth monitoring including Doppler, fetal well-being evaluation) were excluded. We used data for all women who had delivered between 2006 and 2014 in France. These examinations were performed either in free-standing or in hospital facilities (public or private). Other imaging procedures (magnetic resonance imaging or tomodensitometric examination) were not included because their number were very low. To describe the global evolution of prenatal ultrasound associated with pregnancy, we also analyzed US examinations not related with the prenatal screening of fetal anomalies. Because the cares provided in public hospitals between 2006 and 2009, were not recorded, we calculated for each type of care (based on its code), the number of cares performed in the following year, by applying the same evolution to the one observed in the private sector (private hospitals, ambulatory).

As in almost all European countries, there is no national registry of congenital anomalies in France. Therefore, for assessing the trends in the probability of prenatal diagnosis of congenital anomalies, we used data from three French regional registries of birth defects. These public organizations identify cases with congenital abnormalities over a defined area (usually an administrative region). Three registries were included: Auvergne, Paris, and La Reunion, all members of EUROCAT, the European network for registries of birth defects[11] and using the standards recommended for this purpose. We included the population of women who gave birth (live birth or fetal loss after 20 WG) or following a TOFPA in the areas covered by these three registries, during the study period (2006-2014). We excluded women not resident in those areas. A case was a fetus with at least one abnormality whatever the pregnancy outcome was. Fetal anomalies where the ones listed by

EUROCAT (which excludes some minor abnormalities with very low medical or esthetic impact)[12]. In each case, the following data was systematically studied: the timing (prenatal or postnatal) of the diagnosis, and the type of procedure which led to the detection (US examination, first trimester screening for fetal aneuploidy using maternal blood test, invasive procedures). As the aim of our study was to focus on the contribution of US examination on the prenatal screening for fetal anomalies, other modalities leading to a prenatal diagnosis of fetal anomalies, i.e. specific Down's syndrome screening, were excluded (estimated risk ≥ 1/250). However, cases associated with a nuchal translucency measurement above the 99th centile or a cervical cystic hygroma were included, as they were considered to be the result of first ultrasound examination. As a matter of fact, a nuchal translucency above 99th centile led to an estimated risk ≥ 1/250 whatever the maternal biochemical markers results[13–15].

The detection rate was defined as the ratio of the number of cases detected prenatally (positive screening) on the total number of cases per year in the registries. The screening was considered positive if the fetal anomaly was suspected by ultrasound during the pregnancy regardless the precise diagnosis done after birth. For multiple abnormalities, the screening was considered positive if at least one had been detected prenatally. The detection rate was also calculated in a secondary analysis for the two sub-groups of cases with and without chromosomal anomalies. The mean maternal age in registries was compared to the national database[16].

We used linear regression to analyze trends in resource use (average number of ultrasound exams) and logistic regression to analyze trends in odds of prenatal diagnosis

over time. All analyses were conducted using Stata 14.0 software (StataCorp, College Station, Texas).

Results

Prenatal detection rate of fetal anomalies

We included 15,989 cases of fetal anomalies (average: 1,777 per year [range: 1,661 – 1,869]) from the registries between 2006 and 2014. These registries covered an average of 54,907 annual births [range: 53,422 – 55,977], representing 6-7% of the total number of births in France. The prevalence of birth defects during the study period was 3.2% and was fairly stable.

Overall, 18% of the cases were associated with a chromosomal anomaly. The most common chromosomal anomaly was Down's syndrome (54.4%). In cases not associated with chromosomal anomalies, 82% were isolated malformations. Outcomes of pregnancies in cases with isolated malformations were a live birth in 88.1%, a TOPFA in 10.8%, and a fetal loss in 1.1% of cases. TOPFA and fetal loss were more frequent in cases with multiple malformations (33.1% and 3.1% respectively). For cases with chromosomal anomalies, pregnancy outcomes were: live birth in 20.5%, TOPFA in 77.1 fetal loss in 2.4%. 1062 cases (6.7%) were excluded from the calculation of the detection rate because they were related to other modalities of detection than ultrasound (mostly the first trimester combined test, less frequently another biologic test or a systematic invasive test).

The global prenatal detection rate of ultrasound screening in the study period was 57.0%, ranging from 53.9% to 58.7% (Table 1). The detection rate was substantially higher for cases associated with chromosomal anomalies, with a mean value of 91.2% [range: 88.4% - 93.2%]. For cases without chromosomal anomalies, the detection rate ranged from 48.2% to 53.4%, and was higher in cases of multiple anomalies (70.4%), than in cases with an isolated anomaly (47.8%). The logistic regression found a decreasing trend for the global prenatal detection rate during the study period (OR=0,985; 95%IC: [0,972; 0,997]; p=0.015). The figure 1 represent this evolution using moving averages (two-year period).

Resources leveraged for the ultrasound screening for fetal anomalies

In the national claims database, we identified between 5888 and 6882 deliveries per year (0.7% to 0.8% of the total national number of deliveries). The mean maternal age in our sample was similar to one's observed in the national database (source: INSEE [16]). In 2014, an average of 4.08 US examinations were performed per pregnancy, regardless the indication for these examinations, compared to 3.78 in 2010. The Table 2 shows the evolution of the number of US examinations for the screening of fetal anomalies per pregnancy between 2006 and 2014; an increase from 2.47 to 2.98 per pregnancy (+20.6%; p=0.005). We observed an increase of all types of US examinations, especially for the surveillance of fetal anomalies, which went up almost three fold during this period. The number of US examinations unrelated to the screening of fetal anomalies increased from 0.90 to 1.10 between 2010 and 2014 with an increase of 18% of dating ultrasounds and of 26% of US examinations performed for fetal growth surveillance. The average number of invasive

procedures related to the US screening was stable during the study period, with an incidence of 0.015 per pregnancy.

We analyzed the trends by subgrouping by the number of US screening examinations performed: ≥4, 3 or ≤2 US examinations. The trend of the proportion of women in each subgroup is presented in figure 2. The percentage of women with ≥4 US examinations increased between 2010 and 2014 (+4.6%) while those monitored according to the guidelines, i.e. three US examinations, decreased by 6%. Moreover, the proportion of women with fewer than three examinations than recommended by the guidelines remained stable. By including US examinations unrelated to the screening for fetal anomalies, this trend was still present, with a decrease of the percentage of women with 3 US examinations (-6.6%) balanced out by those with ≥4 (+5.1%).

Discussion

Using population-based data in France, we found that the average number of ultrasounds increased over the period 2006 and 2014, whereas the proportion of cases that were prenatally diagnosed did not. The average number of ultrasounds increased from 2.47 to 2.98 per pregnancy during the study period whereas the overall proportion of cases that were prenatally diagnosed was approximately 60% and remained essentially stable over time. Together, these results suggest that there was an increase in the use of resources for prenatal diagnosis of congenital anomalies by ultrasound without an increase in its effectiveness as measured by the proportion of congenital anomalies that were prenatally diagnosed by ultrasound.

The 60% detection rate observed pertained to the detection of fetal anomalies using ultrasound only. Consequently, cases detected by other modalities were not taken into account (mostly the first trimester combined test with NT < 99th), representing additional 7% of cases each year. Therefore, the global detection rate including all modalities of prenatal detection is expected to be slightly higher. Ultrasound screening is highly effective detecting malformations associated with chromosomal anomalies, with an average detection rate of 90.8%. Two-thirds of these cases were detected at first trimester US examination. This is of importance, because in these cases, most of the patients opt for TOPFA, which in return reduces the maternal morbidity when performed in earlier stage of pregnancy.

The stability of the detection rate of fetal anomalies we observed contrasts with the continuous increase (+20.6%) of the number of US examinations performed between 2006 and 2014. This increase did not benefit all the women as we observed that this increase was observed almost only in the sub group of women benefiting of four or more US examinations per pregnancy. This observation corresponds the results of the French National Perinatal Survey, which reported an increase in the average number of US examinations performed per pregnancy from 4.0 in 1995 to 5.0 in 2010 and 5.5 in 2016 (+10%)[17]. Similarly, we observed an increase of 8.2% between 2010 and 2014, considering all categories of US examinations. Additionally, in the French National Perinatal Survey, the proportion of women on whom more than 6 US examinations were performed during their pregnancy increased from 15.8% in 1995 to 35.9% in 2016. In parallel, the proportion of pregnant women with 3 US examinations decreased from 40.4% en 2003 to 24.3% in 2016. It should be mentioned that in the French National Perinatal Survey the number of US examination is self-reported. Whether some of these US examinations that were performed during consultations or not, should have not been taken into account as a systematic US

examination. We ought to remember that this survey is based on self-reporting data. It is almost impossible to know what kind of US examinations was performed.

Previous studies have reported the trends in the prenatal detection rate of fetal anomalies with slightly different detection rates on specific abnormalities among European regions enrolled in the EUROCAT network[18–24]. One of our strengths is that we matched data from different registries to estimate the global prenatal detection rate in France. Additionally, our study focused on the contribution of US alone whereas other studies usually include all the modalities of detection of fetal anomalies. As the specific screening for aneuploidies is in constant evolution (from sequential to combined test to non-invasive testing using cell free DNA in the maternal plasma), our goal was to focus on US only.

Our study has certain limitations and caveats. One caveat is related to the lack of exact correspondence between the study population used for looking at trends in resource use (number of US examinations) vs. the study population for assessing trends in effectiveness of prenatal diagnosis (proportion of cases prenatally diagnosed). In effect, the study population for looking at resource use was the 1% nationally representative sample of pregnant women in the EGB during the study period, whereas the study population used for assessing trends in effectiveness of prenatal diagnostic services (proportion of cases prenatally diagnosed) corresponded to that of the population bases (catchment areas) for the three registries. It is possible that the trends in resource use might be different for the subsample of the French population that resided in the catchment areas of the three registries. However, we have neither a priori reasons nor empirical evidence to suggest that this should be the case. Moreover, the prenatal diagnosis practices and policies are mainly decided at the national level. Hence, we do not believe that this lack of exact

correspondence between our study populations for assessing trends in resource use vs. effectiveness could have biased our results in one way or another.

The development of US screening and its wide-spread use in France during the eighties led to a significant improvement of the prenatal detection rate of fetal anomalies. However, stagnation was observed from 2000s[25]. Our results confirm that stagnation in the detection rate. In parallel, we observed a significant increase of the number of US examinations performed. In addition, we observed that this increase did not benefit all the women. Conversely, the increase was even more pronounced in the sub group of women receiving more than recommended. This accentuates the inequality of cares received even further.

Conclusion

Our study has shown that even though the number of ultrasounds per pregnancy increased over time, the prenatal detection rate of fetal anomalies has not increased in recent years. These data suggest that there is a need to implement policies to improve the efficacy of ultrasound examination for prenatal diagnosis of congenital anomalies, including more high-quality training programs.

Tables and figures

Table 1. Fetal malformation detection rate between 2006 and 2014 by ultrasound screening. P-values for b-logit tests of the detection rate by year.

Table 2. Number of ultrasound procedures per pregnancy between 2006 and 2014. (T1: first trimester, T2: second trimester, T3: third trimester). P-values for simple linear regression of the number of procedures per pregnancy by year.

Figure 1. Evolution of the global ultrasound prenatal detection rate of birth defects during the study period using moving averages (two-year period).

Figure 2. Proportion of screening ultrasound examinations performed during pregnancy in three subgroups. Group A: 3 *ultrasound* examinations (thin line), Group B: 2 or less ultrasound examinations (bold line) and Group C: 4 or more ultrasound examinations (dotted line).

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Contributorship statement

CF, BK, JMJ and IDZ conceptualized the study and designed the analysis. FD was certified for the EGB database access. CF, FD, BK, LG, HR and IP collected the data. All authors contributed to perform the analysis. CF, FD, BK, JMJ, LG and IDZ wrote the final manuscript. JMJ and IDZ were the guarantor of the study.

Competing interest statement

Authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Funding statement

No funds were raised for this study.

Transparency statement

Authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Data sharing statement, details of ethics approval

It was a time-trend observation on aggregated data, provided by an analysis on anonymised individual data, and didn't require ethical approve. The EGB analysis, part of the SNIIRAM

and property of the CNAMTS, was performed after INSERM approval and is covered by the *Commission Nationale de l'Informatique et des Libertés (CNIL*) (accords CNIL AT/CPZ/SVT/JB/DP/CR05222O du 14/06/2005 et DP/CR071761 du 28/08/2007).

References

1. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008 Jan 11;57(1):1–5.

2. Lee K, Khoshnood B, Chen L, Wall SN, Cromie WJ, Mittendorf RL. Infant mortality from congenital malformations in the United States, 1970-1997. Obstet Gynecol. 2001 Oct;98(4):620–7.

3. Hatton F, Bouvier-Colle MH, Blondel B, Pequignot F, Letoullec A. [Trends in infant mortality in France: frequency and causes from 1950 to 1997]. Arch Pediatr Organe Off Soc Francaise Pediatr. 2000 May;7(5):489–500.

4. Matthews TJ, MacDorman MF, Thoma ME. Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set. Natl Vital Stat Rep Cent Dis Control Prev Natl Cent Health Stat Natl Vital Stat Syst. 2015 Aug 6;64(9):1–30.

5. Sureau C, Henrion R. Rapport du Comité National Technique de l'Echographie de dépistage prénatal. 2005.

6. Arrêté du 23 juin 2009 fixant les règles de bonnes pratiques en matière de dépistage et de diagnostic prénatals avec utilisation des marqueurs sériques maternels de la trisomie 21. Source: internet. Avalable on <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000020814373, le 03/09/2017>.

7. LOI no 94-654 du 29 juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal. Source : internet. Avalable on <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000549618&categorieLien=id>.

8. LOI no 2001-588 du 4 juillet 2001 relative à l'interruption volontaire de grossesse et à la contraception. Source: internet. Avalable on <http://admi.net/jo/20010707/MESX0000140L.html le 03/09/2017>.

9. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Oct;65 Suppl 4:S149–67.

10. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954–62.

11. Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. Paper 1: The EUROCAT network--organization and processes. Birt Defects Res A Clin Mol Teratol. 2011 Mar;91 Suppl 1:S2-15.

12. EUROCAT guide 1.4, section 3.2. Minor anomalies for exclusion. Source: internet. Date: 11/11/2017. Link: http://www.eurocat-network.eu/content/Section%203.2-%2027_Oct2016.pdf.

13. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. BMJ. 1992 Apr 4;304(6831):867–9.

14. Taipale P, Hiilesmaa V, Salonen R, Ylöstalo P. Increased nuchal translucency as a marker for fetal chromosomal defects. N Engl J Med. 1997 Dec 4;337(23):1654–8.

15. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet Lond Engl. 1998 Aug 1;352(9125):343–6.

16. INSEE, average age of mothers at birth. Source: internet. Date: 11/11/2017. Link: https://www.insee.fr/fr/statistiques/2381390#tableau-Donnes.

17. Blondel B, Coulm B, Bonnet C, Goffinet F, Le Ray C, National Coordination Group of the National Perinatal Surveys. Trends in perinatal health in metropolitan France from 1995 to 2016: Results from the French National Perinatal Surveys. J Gynecol Obstet Hum Reprod. 2017 Oct 11;

18. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, et al. Prenatal diagnosis of severe structural congenital malformations in Europe. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2005 Jan;25(1):6–11.

19. Garne E, Loane M, Wellesley D, Barisic I, Eurocat Working Group. Congenital hydronephrosis: prenatal diagnosis and epidemiology in Europe. J Pediatr Urol. 2009 Feb;5(1):47–52.

20. Boyd PA, Devigan C, Khoshnood B, Loane M, Garne E, Dolk H, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG Int J Obstet Gynaecol. 2008 May;115(6):689–96.

21. Pedersen RN, Calzolari E, Husby S, Garne E, EUROCAT Working group. Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. Arch Dis Child. 2012 Mar;97(3):227–32.

22. Garne E, Eurocat Working Group. Prenatal diagnosis of six major cardiac malformations in Europe--a population based study. Acta Obstet Gynecol Scand. 2001 Mar;80(3):224–8.

23. Boyd PA, Loane M, Garne E, Khoshnood B, Dolk H, EUROCAT working group. Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. Eur J Hum Genet EJHG. 2011 Feb;19(2):231–4.

24. Khoshnood B, De Vigan C, Vodovar V, Goujard J, Goffinet F. A population-based evaluation of the impact of antenatal screening for Down's syndrome in France, 1981-2000. BJOG Int J Obstet Gynaecol. 2004 May;111(5):485–90.

25. Khoshnood B, Lelong N, Lecourbe A, Ballon M, Goffinet F. Registre des malformations congénitales de Paris. Surveillance épidémiologique et diagnostic prénatal des malformations : évolution sur 35 ans (1981-2014). 2014.

Tables

Table 1. Fetal malformation detection rate between 2006 and 2014 by ultrasound screening. P-values for b-logit tests of the detection rate by year.

	Global detection rate	Detection rate for cases without chromosomal abnormalities	Detection rate for cases with chromosomal abnormalities
2006	58.2%	52.2%	91.3%
2007	57.9%	52.3%	90.9%
2008	58.7%	52.6%	93.2%
2009	57.2%	51.9%	88.4%
2010	57.2%	52.4%	92.3%
2011	57.8%	53.4%	90.5%
2012	53.9%	48.2%	90.2%
2013	57.3%	52.8%	93.2%
2014	55.2%	50.2%	90.9%
p-value	0.015	0.170	0.975

Table 2. Number of ultrasound procedures per pregnancy between 2006 and 2014. (T1: first trimester, T2: second trimester, T3: third trimester). P-values for simple linear regression of the number of procedures per pregnancy by year.

Procedures	2006	2007	2008	2009	2010	2011	2012	2013	2014	p-value
T1 Ultrasound	0,73	0,79	0,92	0,88	0,89	0,89	0,87	0,88	0,88	0,102
T2 Ultrasound	0,84	0,80	0,96	0,92	0,94	0,95	0,94	0,95	0,95	0,033
T3 Ultrasound	0,82	0,74	0,89	0,85	0,88	0,87	0,87	0,89	0,87	0,102
Surveillance	0,07	0,11	0,11	0,13	0,14	0,17	0,18	0,24	0,26	0,003
Fetal Heart	0,01	0,02	0,01	0,02	0,02	0,02	0,02	0,02	0,03	<0,001
Total	**2,47**	**2,45**	**2,89**	**2,79**	**2,87**	**2,90**	**2,89**	**2,98**	**2,98**	**0,005**

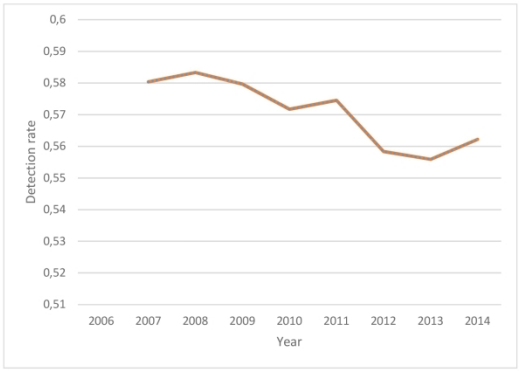

Figure 1. Evolution of the global ultrasound prenatal detection rate of birth defects during the study period using moving averages (two-year period).

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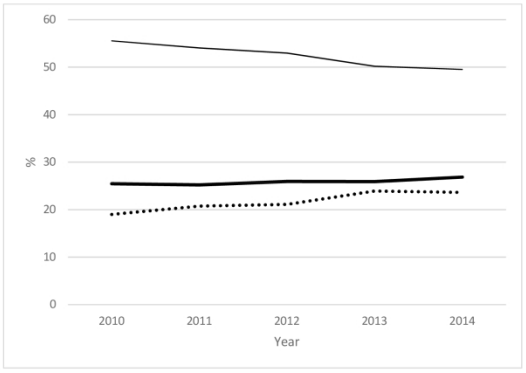

Figure 2. Proportion of screening ultrasound examinations performed during pregnancy in three subgroups. Group A: 3 ultrasound examinations (thin line), Group B: 2 or less ultrasound examinations (bold line) and Group C: 4 or more ultrasound examinations (dotted line).

209x297mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	X
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	X
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*X*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*X*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8-9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Trends in resource use and effectiveness of ultrasound detection of fetal structural anomalies in France: a multiple registry-based study.

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Trends in resource use and effectiveness of ultrasound detection of fetal structural anomalies in France: a multiple registry-based study.

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Abstract

Objective: To analyze trends in the number of ultrasound examinations in relation to the effectiveness of prenatal detection of birth defects using population-based data in France.

Design: A multiple registry-based study of time trends in resource use (number of ultrasounds) and effectiveness (proportion of cases prenatally diagnosed)

Setting: France. Three registries of congenital anomalies and claims data on ultrasounds for all pregnant women.

Participants: Two samples of pregnant women. The effectiveness was assessed using data from three French birth defect registries. Resource use for ultrasound screening was based on the French national healthcare database.

Main outcome measures: Prenatal diagnosis (effectiveness) and average number of ultrasounds (resource use). Statistical analyses included linear and logistic regression models to assess trends in resource use and effectiveness of prenatal testing, respectively.

Results: The average number of ultrasound examinations per pregnancy significantly increased over the study period, from 2.47 in 2006 to 2.98 in 2014 (p=0.005). However, there was no significant increase in the odds of prenatal diagnosis. The probability of prenatal diagnosis was substantially higher for cases associated with a chromosomal anomaly (91.2%) than those without (51.8%). However, there was no evidence of an increase in prenatal detection of either over time.

Conclusions: The average number of ultrasound examinations per pregnancy increased over time whereas the probability of prenatal diagnosis of congenital anomalies did not. Hence, there is a need to implement policies such as high-quality training programs, which can improve the efficiency of US examinations for prenatal detection of congenital anomalies.

Keywords: Birth defect; Ultrasound; Effectiveness; Prenatal diagnosis.

Strengths and limitations of this study:

- We observed the chronological trend of the French ultrasound birth defect screening program.
- We measured the detection rate of birth defects and the number of screening ultrasound per pregnancy.
- We used two large data sources: national registries of birth defect and the national claims database.
- We excluded birth defects detected by other methods.
- There was no linkage between records of patients in the two data sources.

Introduction

Congenital abnormalities occur in approximately 2 percent of all live births[1]. They are one of the leading causes of infant mortality and morbidity in industrialized countries[2–4]. Prenatal diagnosis of congenital abnormalities is a prerequisite for adequate prenatal counseling and management and in the case of severe abnormalities without curative option it offers the possibility of Termination of Pregnancy for Fetal Abnormality (TOPFA).

In France, prenatal screening for the detection of fetal anomalies is organized by laws and guidelines which apply to both free-standing clinics and public or private hospitals. In addition, all sonographers are certified by a specific initial training. Three ultrasound (US) screening examinations are recommended in singleton pregnancies at 11-14 weeks', 20-25 weeks' and 30-35 weeks' gestation (WG)[5]. Besides this ultrasound examination, a first trimester combined test is offered to each pregnant woman for the evaluation of risk for Down's syndrome[6]. When a fetal anomaly is suspected, patients are referred to specialized referral centers for further investigations[7]. There are 49 referral centers for prenatal diagnosis in France and its territories. The regional implementation of centers is determined by the number of births. TOFPA is authorized up to the end of the pregnancy, at the request of the mother, once two experts have certified the severity of the fetal anomaly[8].

The French national health insurance covers the entire cost of the prenatal screening of fetal anomalies. However, the number of scans performed per pregnancy and its result in terms of prenatal detection rate for fetal anomalies have never, to our knowledge been studying so far, while representing a significant amount of public resources either in France or in other countries

Our objective was to assess the effectiveness of ultrasound prenatal screening for fetal anomalies by measuring the trend in the number of US examinations for the detection of fetal anomalies and the proportion of anomalies were prenatally diagnosed between 2006 and 2014, in France.

Data and methods

Data sources, Patients

We used two data sources for our study. In order to identify trends in the average number of ultrasound examinations per pregnancy, we used the national claims database: the Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM)[9]. Our data source was the *Echantillon Généraliste des Bénéficiaires* (EGB), a permanent representative sample of 1/97 of the individuals covered by the French Health Insurance System[10]. This representative sample does not allow however region-specific analyses. Our analysis on anonymised individual data did not require ethical approve. The claims analysis was authorized by the French institute for medical research (INSERM) and is covered by the *Commission Nationale de l'Informatique et des Libertés (CNIL*) (accords CNIL AT/CPZ/SVT/JB/DP/CR05222O du 14/06/2005 et DP/CR071761 du 28/08/2007).

We used data for all women who had delivered between 2006 and 2014 in France. The claims data base identifies each episode of care by a code. Codes used to identify US examinations performed during the pregnancy inform on the indication. We included scans for the detection of fetal anomalies (systematic 1st, 2nd and 3rd trimester US examinations) or scans for the

monitoring of a known fetal anomaly, fetal echocardiography. These scans were performed either in free-standing or in hospital facilities (public or private).

Examinations with no relation to the prenatal detection of fetal anomalies (dating US examinations before 11 WG, US examinations for fetal growth monitoring including Doppler, fetal well-being evaluation) were used to describe the global trend in pregnancy-associated ultrasound examinations but excluded from the analysis of US screening for fetal anomalies. Other imaging procedures (magnetic resonance imaging or tomodensitometric examination) were excluded. Because ultrasound examinations performed in public hospitals between 2006 and 2009 were not recorded, we applied to hospital scans the same rate of increase as observed in private hospitals and free standing imaging clinics.

As in almost all European countries, there is no national registry of congenital anomalies in France. To assess the trends in the probability of prenatal detection of congenital anomalies, we used data from three French regional registries of birth defects. These public organizations identify cases with congenital anomalies over a predefined area (usually an administrative region). We included three registries: Auvergne, Paris, and La Reunion, all members of EUROCAT, the European network for registries of birth defects[11], and using the standards recommended for this purpose. We included the population of women who gave birth (live birth or fetal loss after 20 WG) or following a TOFPA in the areas covered by these three registries, during the study period (2006-2014). We excluded women not resident in those areas. A case was defined as a fetus with at least one abnormality whatever the pregnancy outcome was. Fetal anomalies where the ones listed by EUROCAT (which excludes some minor abnormalities with very low medical or esthetic impact)[12]. In each case, we systematically extracted the time (prenatal or postnatal) of

detection, and the type of procedure which led to the detection (US examination, first trimester screening for fetal aneuploidy using maternal blood test, invasive procedures). As the aim of our study was to identify the contribution of US examination on detection of fetal anomalies, other modalities leading to a prenatal diagnosis of fetal anomalies, i.e. specific Down's syndrome screening, were excluded (estimated risk ≥ 1/250). However, cases associated with a nuchal translucency measurement above the 99th centile or a cervical cystic hygroma were included, as they were considered to be the result of first ultrasound examination since a nuchal translucency above 99th centile led to an estimated risk ≥ 1/250 whatever the maternal biochemical markers results[13–15].

Pooling the data of the three registries, the overall detection rate was defined as the ratio of the number of cases detected prenatally (positive screening) on the total number of cases per year. The screening was considered positive if the fetal anomaly was suspected by ultrasound during the pregnancy regardless the precise diagnosis after birth. For multiple abnormalities, the screening was considered positive if at least one had been detected prenatally. The detection rate was also calculated in a secondary analysis for the two sub-groups of cases with and without chromosomal anomalies.

We used linear regression to analyze trends in resource use (average number of ultrasound exams) and logistic regression to analyze trends in odds of prenatal detection over time. All analyses were conducted using Stata 14.0 software (StataCorp, College Station, Texas).

Results

Prenatal detection rate of fetal anomalies

We included 15,989 cases of fetal anomalies (average: 1,777 per year [range: 1,661 – 1,869]) from the registries between 2006 and 2014. These registries covered an average of 54,907 annual births [range: 53,422 – 55,977], representing 6-7% of the total number of births in France. The prevalence of birth defects during the study period was 3.2% and was fairly stable.

Overall, 18% of the cases were associated with a chromosomal anomaly. The most common chromosomal anomaly was Down's syndrome (54.4%). In cases not associated with chromosomal anomalies, 82% were isolated malformations. Outcomes of pregnancies in cases with isolated malformations were a live birth in 88.1%, a TOPFA in 10.8%, and a fetal loss in 1.1% of cases. TOPFA and fetal loss were more frequent in cases with multiple malformations (33.1% and 3.1% respectively). For cases with chromosomal anomalies, pregnancy outcomes were: live birth in 20.5%, TOPFA in 77.1 fetal loss in 2.4%. 1062 cases (6.7%) were excluded from the calculation of the detection rate because they were related to other modalities of detection than ultrasound (mostly the first trimester combined test, less frequently another biological test or a systematic invasive test).

The overall prenatal detection rate (including cases with and without chromosomal anomalies) of ultrasound screening in the study period was 57.0%, ranging from 53.9% to 58.7% (Table 1). Consequently, 43% of cases were detected postnataly. The detection rate was substantially higher for cases associated with chromosomal anomalies, with a mean value of

91.2% [range: 88.4% - 93.2%]., The detection rate for cases without chromosomal anomalies ranged from 48.2% to 53.4%, and was higher in cases of multiple anomalies (70.4%), than in cases with an isolated anomaly (47.8%). The logistic regression found a decreasing trend for the overall prenatal detection rate during the study period (OR=0,985; 95%IC: [0,972; 0,997]; p=0.015). Figure 1 represent this trend using moving averages (two-year period).

Resources leveraged for the ultrasound screening for fetal anomalies

In the 1/97 sample of the national claims database, we identified between 5,888 and 6,882 deliveries per year (0.7% to 0.8% of the total national number of deliveries). The mean maternal age in our sample was similar to the age observed in the national database (source: INSEE[16]). In 2014, an average of 4.08 US examinations were performed per pregnancy, for screening and other indications, compared to 3.78 in 2010. Table 2 shows the trend in the number of US examinations for the screening of fetal anomalies per pregnancy only. Between 2006 and 2014; we found an increase from 2.47 to 2.98 per pregnancy (+20.6%; p=0.005). We observed an increase of all types of US examinations, especially for the surveillance of fetal anomalies, which went up almost three fold during this period. The number of US examinations unrelated to the screening of fetal anomalies increased from 0.90 to 1.10 per pregnancy between 2010 and 2014, with an increase of 18% for dating ultrasounds and of 26% of US examinations performed for fetal growth surveillance. The average number of invasive procedures related to the US screening was stable during the study period, with an incidence of 0.015 per pregnancy.

We analyzed the trends for three subgroups defined by the number of scans performed per pregnancy: ≥4, 3 or ≤2. The trend in each subgroup is presented in figure 2. The percentage of women with ≥4 US examinations increased between 2010 and 2014 (+4.6%) while those monitored according to the guidelines, i.e. three US examinations, decreased by 6%. Moreover, the proportion of women with fewer than three examinations than recommended by the guidelines remained stable.

Discussion

Using population-based data in France, we found that the average number of ultrasound examinations for the detection of fetal anomalies increased over the period 2006 and 2014, whereas the proportion of cases that were prenatally detected did not. The average number of scans increased from 2.47 to 2.98 per pregnancy during the study period whereas the overall proportion of fetal anomalies detected prenatally was approximately 60% and remained essentially stable over time diagnosed. These results suggest that that the increase in the use of resources for prenatal detection of congenital anomalies by ultrasound was not matched by increase in the proportion of congenital anomalies that were prenatally detected by ultrasound.

Our findings do not preclude that the proportion of cases that were prenatally diagnosed for some specific anomalies might have increased over time. However, given the essentially constant overall proportion of cases that were prenatally diagnosed, any such improvements

must have been restricted to a limited number of anomalies and would have been relatively small in magnitude.

The 60% detection rate pertained to ultrasound only. Consequently, cases detected by other modalities were not taken into account (mostly the first trimester combined test with NT < 99th), representing additional 7% of cases each year. Therefore, the global detection rate including all modalities of prenatal detection is expected to be slightly higher. Ultrasound screening is highly effective detecting malformations associated with chromosomal anomalies, with an average detection rate of 90.8%. Two-thirds of these cases were detected at first trimester US examination. This is of importance, because in these cases, most of the patients opt for TOPFA, which in return reduces the maternal morbidity when performed in earlier stage of pregnancy.

The stability of the detection rate of fetal anomalies that we observed contrasts with the continuous increase (+20.6%) of the number of US examinations performed between 2006 and 2014. This increase did not benefit to all women. Indeed, it occurred almost only in the sub group of women benefiting of four or more US examinations per pregnancy. This observation corresponds the results of the French National Perinatal Survey, which reported an increase in the average number of US examinations performed per pregnancy from 4.0 in 1995 to 5.0 in 2010 and 5.5 in 2016 (+10%)[17]. Similarly, we observed an increase of 8.2% between 2010 and 2014, considering all categories of US examinations. Additionally, in the French National Perinatal Survey, the proportion of women on whom more than 6 US examinations were performed during their pregnancy increased from 15.8% in 1995 to 35.9% in 2016. In parallel, the proportion of pregnant women with 3 US examinations decreased from 40.4% in 2003 to 24.3% in 2016. This

survey is based on self-reporting data which makes it almost impossible to know what kind of US examinations was performed. In our study, the database only contained codes used by care providers to record US examinations, but no other clinical information or the precise indications for these examinations.

Previous studies have reported the trends in the prenatal detection rate of fetal anomalies with slightly different detection rates on specific abnormalities among European regions enrolled in the EUROCAT network[18–24]. One of our strengths is that we combined data from different registries to estimate the global prenatal detection rate in France. Additionally, our study focused on the contribution of US alone whereas other studies usually include all the modalities of detection of fetal anomalies, which makes it difficult to identify the contribution of US as the specific screening for aneuploidies is in constant evolution (from sequential to combined test to non-invasive testing using cell free DNA in the maternal plasma).

Our study had limitations and caveats. One is related to the lack of exact correspondence between the study population used for identifying trends in resource use (number of US examinations) vs. the study population for assessing trends in effectiveness of prenatal detection (proportion of cases prenatally detected). It is possible that the trends in resource use might be different for the subsample of the French population that resided in the catchment areas of the three registries. However, we have neither a priori reasons nor empirical evidence to suggest that this should be the case. Moreover, the prenatal diagnosis practices and policies are mainly decided at the national level. Hence, we do not believe that this lack of exact correspondence between our study populations for assessing trends in resource use vs. effectiveness could have biased our results in one way or another.

Due to a modification in the calculation of the hospital's funding between 2006 and 2009, the number of US examinations performed during this period in public hospitals was not recorded and had to be estimated. However, we have no reason to think there were differences between private and public providers during this period. In addition, public hospitals account for less than 20% of US examinations, thus limiting a potential bias resulting from the estimation we have made for this period.

The development of US screening and its wide-spread use in France during the eighties led to a significant improvement of the prenatal detection rate of fetal anomalies. However, stagnation was observed from 2000s[25]. Our results confirm that stagnation in the detection rate. In parallel, we observed a significant increase of the number of US examinations performed. In addition, we observed that this increase did not benefit all the women. Conversely, the increase was even more pronounced in the sub group of women receiving more than recommended. The ecological design of our study limits the interpretation of the observed trends. However, the trend indicated a further increase in inequality of care for the surveillance of pregnant women.

Conclusion

Our study has shown that even though the number of ultrasound examinations per pregnancy increased over time, the prenatal detection rate of fetal anomalies has not increased in recent years. These data suggest that there is a need to implement policies to improve the efficacy of ultrasound examination for prenatal diagnosis of congenital anomalies, including more high-quality training programs.

Tables and figures

Table 1. Fetal malformation detection rate between 2006 and 2014 by ultrasound screening. P-values for b-logit tests of the detection rate by year.

Table 2. Number of screening ultrasound examination per pregnancy between 2006 and 2014. (T1: first trimester, T2: second trimester, T3: third trimester). P-values for simple linear regression of the number of procedures per pregnancy by year.

Figure 1. Evolution of the overall ultrasound prenatal detection rate of birth defects during the study period using moving averages (two-year period).

Figure 2. Proportion of screening ultrasound examinations performed during pregnancy in three subgroups. Group A: 3 *ultrasound* examinations (thin line), Group B: 2 or less ultrasound examinations (bold line) and Group C: 4 or more ultrasound examinations (dotted line).

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Contributorship statement

All authors listed for this manuscript fulfill the ICMJE criteria.

CF, BK, JMJ and IDZ conceptualized the study and designed the analysis. FD was certified for the EGB database access. CF, FD, BK, LG, HR and IP collected the data. All authors contributed to perform the analysis. CF, FD, BK, JMJ, LG and IDZ wrote the final manuscript. JMJ and IDZ were the guarantor of the study.

Competing interest statement

Authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Funding statement

No funds were raised for this study.

Transparency statement

Authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Data sharing statement, details of ethics approval

There is no unpublished data.

It was a time-trend observation on aggregated data, provided by an analysis on anonymised individual data, and didn't require ethical approve. The EGB analysis, part of the SNIIRAM and property of the CNAMTS, was performed after INSERM approval and is covered by the *Commission Nationale de l'Informatique et des Libertés (CNIL*) (accords CNIL AT/CPZ/SVT/JB/DP/CR05222O du 14/06/2005 et DP/CR071761 du 28/08/2007).

Patient and public involvement statement

There was no patient nor public involvement in the design of the study.

References

1. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008 Jan 11;57(1):1–5.

2. Lee K, Khoshnood B, Chen L, Wall SN, Cromie WJ, Mittendorf RL. Infant mortality from congenital malformations in the United States, 1970-1997. Obstet Gynecol. 2001 Oct;98(4):620–7.

3. Hatton F, Bouvier-Colle MH, Blondel B, Pequignot F, Letoullec A. [Trends in infant mortality in France: frequency and causes from 1950 to 1997]. Arch Pediatr Organe Off Soc Francaise Pediatr. 2000 May;7(5):489–500.

4. Matthews TJ, MacDorman MF, Thoma ME. Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set. Natl Vital Stat Rep Cent Dis Control Prev Natl Cent Health Stat Natl Vital Stat Syst. 2015 Aug 6;64(9):1–30.

5. Sureau C, Henrion R. Rapport du Comité National Technique de l'Echographie de dépistage prénatal. 2005.

6. Arrêté du 23 juin 2009 fixant les règles de bonnes pratiques en matière de dépistage et de diagnostic prénatals avec utilisation des marqueurs sériques maternels de la trisomie 21. Source: internet. Avalable on <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000020814373, le 03/09/2017>.

7. LOI no 94-654 du 29 juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal. Source : internet. Avalable on <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000549618&categorieLien=id>.

8. LOI no 2001-588 du 4 juillet 2001 relative à l'interruption volontaire de grossesse et à la contraception. Source: internet. Avalable on <http://admi.net/jo/20010707/MESX0000140L.html le 03/09/2017>.

9. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Oct;65 Suppl 4:S149–67.

10. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954–62.

11. Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. Paper 1: The EUROCAT network--organization and processes. Birt Defects Res A Clin Mol Teratol. 2011 Mar;91 Suppl 1:S2-15.

12. EUROCAT guide 1.4, section 3.2. Minor anomalies for exclusion. Source: internet. Date: 11/11/2017. Link: http://www.eurocat-network.eu/content/Section%203.2-%2027_Oct2016.pdf.

13. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. BMJ. 1992 Apr 4;304(6831):867–9.

14. Taipale P, Hiilesmaa V, Salonen R, Ylöstalo P. Increased nuchal translucency as a marker for fetal chromosomal defects. N Engl J Med. 1997 Dec 4;337(23):1654–8.

15. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet Lond Engl. 1998 Aug 1;352(9125):343–6.

16. INSEE, average age of mothers at birth. Source: internet. Date: 11/11/2017. Link: https://www.insee.fr/fr/statistiques/2381390#tableau-Donnes.

17. Blondel B, Coulm B, Bonnet C, Goffinet F, Le Ray C, National Coordination Group of the National Perinatal Surveys. Trends in perinatal health in metropolitan France from 1995 to 2016: Results from the French National Perinatal Surveys. J Gynecol Obstet Hum Reprod. 2017 Oct 11;

18. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, et al. Prenatal diagnosis of severe structural congenital malformations in Europe. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2005 Jan;25(1):6–11.

19. Garne E, Loane M, Wellesley D, Barisic I, Eurocat Working Group. Congenital hydronephrosis: prenatal diagnosis and epidemiology in Europe. J Pediatr Urol. 2009 Feb;5(1):47–52.

20. Boyd PA, Devigan C, Khoshnood B, Loane M, Garne E, Dolk H, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG Int J Obstet Gynaecol. 2008 May;115(6):689–96.

21. Pedersen RN, Calzolari E, Husby S, Garne E, EUROCAT Working group. Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. Arch Dis Child. 2012 Mar;97(3):227–32.

22. Garne E, Eurocat Working Group. Prenatal diagnosis of six major cardiac malformations in Europe--a population based study. Acta Obstet Gynecol Scand. 2001 Mar;80(3):224–8.

23. Boyd PA, Loane M, Garne E, Khoshnood B, Dolk H, EUROCAT working group. Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. Eur J Hum Genet EJHG. 2011 Feb;19(2):231–4.

24. Khoshnood B, De Vigan C, Vodovar V, Goujard J, Goffinet F. A population-based evaluation of the impact of antenatal screening for Down's syndrome in France, 1981-2000. BJOG Int J Obstet Gynaecol. 2004 May;111(5):485–90.

25. Khoshnood B, Lelong N, Lecourbe A, Ballon M, Goffinet F. Registre des malformations congénitales de Paris. Surveillance épidémiologique et diagnostic prénatal des malformations : évolution sur 35 ans (1981-2014). 2014.

Tables

Table 1. Fetal malformation detection rate between 2006 and 2014 by ultrasound screening. P-values for b-logit tests of the detection rate by year.

	Overall detection rate	Detection rate for cases without chromosomal abnormalities	Detection rate for cases with chromosomal abnormalities
2006	58.2%	52.2%	91.3%
2007	57.9%	52.3%	90.9%
2008	58.7%	52.6%	93.2%
2009	57.2%	51.9%	88.4%
2010	57.2%	52.4%	92.3%
2011	57.8%	53.4%	90.5%
2012	53.9%	48.2%	90.2%
2013	57.3%	52.8%	93.2%
2014	55.2%	50.2%	90.9%
p-value	0.015	0.170	0.975

Table 2. Number of screening ultrasound examinations per pregnancy, between 2006 and 2014. (T1: first trimester, T2: second trimester, T3: third trimester). P-values for simple linear regression of the number of procedures per pregnancy by year.

Procedures	2006	2007	2008	2009	2010	2011	2012	2013	2014	p-value
T1 Ultrasound	0,73	0,79	0,92	0,88	0,89	0,89	0,87	0,88	0,88	0,102
T2 Ultrasound	0,84	0,80	0,96	0,92	0,94	0,95	0,94	0,95	0,95	0,033
T3 Ultrasound	0,82	0,74	0,89	0,85	0,88	0,87	0,87	0,89	0,87	0,102
Surveillance	0,07	0,11	0,11	0,13	0,14	0,17	0,18	0,24	0,26	0,003
Fetal Heart	0,01	0,02	0,01	0,02	0,02	0,02	0,02	0,02	0,03	<0,001
Total	**2,47**	**2,45**	**2,89**	**2,79**	**2,87**	**2,90**	**2,89**	**2,98**	**2,98**	**0,005**

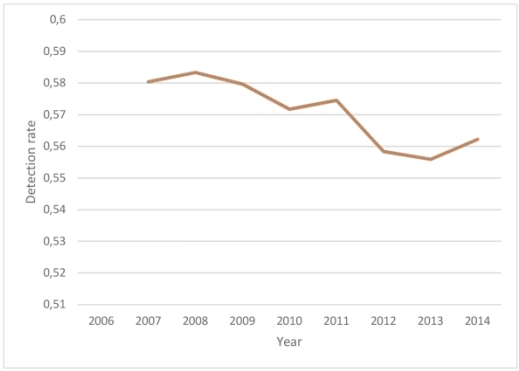

figure 1

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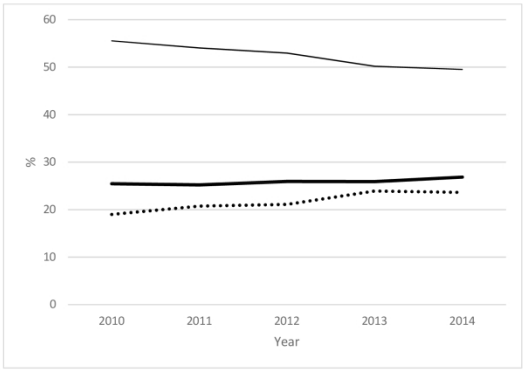

Figure 2. Proportion of screening ultrasound examinations performed during pregnancy in three subgroups. Group A: 3 ultrasound examinations (thin line), Group B: 2 or less ultrasound examinations (bold line) and Group C: 4 or more ultrasound examinations (dotted line).

209x297mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	X
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	X
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*X*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*X*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8-9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Trends in resource use and effectiveness of ultrasound detection of fetal structural anomalies in France: a multiple registry-based study.

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Secondary Subject Heading:	Health services research, Public health
Keywords:	Birth defect, Ultrasound < RADIOLOGY & IMAGING, Effectiveness, Prenatal diagnosis < OBSTETRICS

Trends in resource use and effectiveness of ultrasound detection of fetal structural anomalies in France: a multiple registry-based study.

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Abstract

Objective: To analyze trends in the number of ultrasound examinations in relation to the effectiveness of prenatal detection of birth defects using population-based data in France.

Design: A multiple registry-based study of time trends in resource use (number of ultrasounds) and effectiveness (proportion of cases prenatally diagnosed)

Setting: France. Three registries of congenital anomalies and claims data on ultrasounds for all pregnant women.

Participants: Two samples of pregnant women. The effectiveness was assessed using data from three French birth defect registries. Resource use for ultrasound screening was based on the French national healthcare database.

Main outcome measures: Prenatal diagnosis (effectiveness) and average number of ultrasounds (resource use). Statistical analyses included linear and logistic regression models to assess trends in resource use and effectiveness of prenatal testing, respectively.

Results: The average number of ultrasound examinations per pregnancy significantly increased over the study period, from 2.47 in 2006 to 2.98 in 2014 (p=0.005). However, there was no significant increase in the odds of prenatal diagnosis. The probability of prenatal diagnosis was substantially higher for cases associated with a chromosomal anomaly (91.2%) than those without (51.8%). However, there was no evidence of an increase in prenatal detection of either over time.

Conclusions: The average number of ultrasound examinations per pregnancy increased over time whereas the probability of prenatal diagnosis of congenital anomalies did not. Hence,

there is a need to implement policies such as high-quality training programs, which can improve the efficiency of US examinations for prenatal detection of congenital anomalies.

Keywords: Birth defect; Ultrasound; Effectiveness; Prenatal diagnosis.

Strengths and limitations of this study:

- We observed the chronological trend of the French ultrasound birth defect screening program.
- We measured the detection rate of birth defects and the number of screening ultrasound per pregnancy.
- We used two large data sources: national registries of birth defect and the national claims database.
- We excluded birth defects detected by other methods.
- There was no linkage between records of patients in the two data sources.

Introduction

Congenital abnormalities occur in approximately 2 percent of all live births[1]. They are one of the leading causes of infant mortality and morbidity in industrialized countries[2–4]. Prenatal diagnosis of congenital abnormalities is a prerequisite for adequate prenatal counseling and management and in the case of severe abnormalities without curative option it offers the possibility of Termination of Pregnancy for Fetal Abnormality (TOPFA).

In France, prenatal screening for the detection of fetal anomalies is organized by laws and guidelines which apply to both free-standing clinics and public or private hospitals. In addition, all physicians (obstetricians or radiologists) or midwives performing screening ultrasound examinations are certified by a degree obtained after a specific initial training. Three ultrasound (US) screening examinations are recommended in singleton pregnancies at 11-14 weeks', 20-25 weeks' and 30-35 weeks' gestation (WG)[5]. Besides this ultrasound examination, a first trimester combined test is offered to each pregnant woman for the evaluation of risk for Down's syndrome[6]. When a fetal anomaly is suspected, patients are referred to specialized referral centers for further investigations[7]. There are 49 referral centers for prenatal diagnosis in France and its territories. The regional implementation of centers is determined by the number of births. TOFPA is authorized up to the end of the pregnancy, at the request of the mother, once two experts have certified the severity of the fetal anomaly[8].

The French national health insurance covers the entire cost of the prenatal screening of fetal anomalies. However, the number of scans performed per pregnancy and its result in terms of prenatal detection rate for fetal anomalies have never, to our knowledge been

studying so far, while representing a significant amount of public resources either in France or in other countries

Our objective was to assess the effectiveness of ultrasound prenatal screening for fetal anomalies by measuring the trend in the number of US examinations for the detection of fetal anomalies and the proportion of anomalies were prenatally diagnosed between 2006 and 2014, in France.

Data and methods

Data sources, Patients

We used two data sources for our study. In order to identify trends in the average number of ultrasound examinations per pregnancy, we used the national claims database: the Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM)[9]. Our data source was the *Echantillon Généraliste des Bénéficiaires* (EGB), a permanent representative sample of 1/97 of the individuals covered by the French Health Insurance System[10]. This representative sample does not allow however region-specific analyses. Our analysis on anonymised individual data did not require ethical approve. The claims analysis was authorized by the French institute for medical research (INSERM) and is covered by the *Commission Nationale de l'Informatique et des Libertés (CNIL*) (accords CNIL AT/CPZ/SVT/JB/DP/CR05222O du 14/06/2005 et DP/CR071761 du 28/08/2007).

We used data for all women who had delivered between 2006 and 2014 in France. The claims data base identifies each episode of care by a code. Codes used to identify US examinations performed during the pregnancy inform on the indication. We included scans

for the detection of fetal anomalies (systematic 1st, 2nd and 3rd trimester US examinations) or scans for the monitoring of a known fetal anomaly, fetal echocardiography. These scans were performed either in free-standing or in hospital facilities (public or private).

Examinations with no relation to the prenatal detection of fetal anomalies (dating US examinations before 11 WG, US examinations for fetal growth monitoring including Doppler, fetal well-being evaluation) were used to describe the global trend in pregnancy-associated ultrasound examinations but excluded from the analysis of US screening for fetal anomalies. Other imaging procedures (magnetic resonance imaging or tomodensitometric examination) were excluded. Because ultrasound examinations performed in public hospitals between 2006 and 2009 were not recorded, we applied to hospital scans the same rate of increase as observed in private hospitals and free standing imaging clinics.

As in almost all European countries, there is no national registry of congenital anomalies in France. To assess the trends in the probability of prenatal detection of congenital anomalies, we used data from three French regional registries of birth defects. These public organizations identify cases with congenital anomalies over a predefined area (usually an administrative region). We included three registries: Auvergne, Paris, and La Reunion, all members of EUROCAT, the European network for registries of birth defects[11], and using the standards recommended for this purpose. We included the population of women who gave birth (live birth or fetal loss after 20 WG) or following a TOFPA in the areas covered by these three registries, during the study period (2006-2014). We excluded women not resident in those areas. A case was defined as a fetus with at least one abnormality whatever the pregnancy outcome was. Fetal anomalies where the ones listed by EUROCAT (which excludes some minor abnormalities with very low medical or esthetic impact)[12]. In each case, we

systematically extracted the time (prenatal or postnatal) of detection, and the type of procedure which led to the detection (US examination, first trimester screening for fetal aneuploidy using maternal blood test, invasive procedures). As the aim of our study was to identify the contribution of US examination on detection of fetal anomalies, other modalities leading to a prenatal diagnosis of fetal anomalies, i.e. specific Down's syndrome screening, were excluded (estimated risk ≥ 1/250). However, cases associated with a nuchal translucency measurement above the 99th centile or a cervical cystic hygroma were included, as they were considered to be the result of first ultrasound examination since a nuchal translucency above 99th centile led to an estimated risk ≥ 1/250 whatever the maternal biochemical markers results[13–15].

Pooling the data of the three registries, the overall detection rate was defined as the ratio of the number of cases detected prenatally (positive screening) on the total number of cases per year. The screening was considered positive if the fetal anomaly was suspected by ultrasound during the pregnancy regardless the precise diagnosis after birth. For multiple abnormalities, the screening was considered positive if at least one had been detected prenatally. The detection rate was also calculated in a secondary analysis for the two sub-groups of cases with and without chromosomal anomalies.

We used linear regression to analyze trends in resource use (average number of ultrasound exams) and logistic regression to analyze trends in odds of prenatal detection over time. All analyses were conducted using Stata 14.0 software (StataCorp, College Station, Texas).

Results

Prenatal detection rate of fetal anomalies

We included 15,989 cases of fetal anomalies (average: 1,777 per year [range: 1,661 – 1,869]) from the registries between 2006 and 2014. These registries covered an average of 54,907 annual births [range: 53,422 – 55,977], representing 6-7% of the total number of births in France. The prevalence of birth defects during the study period was 3.2% and was fairly stable.

Overall, 18% of the cases were associated with a chromosomal anomaly. The most common chromosomal anomaly was Down's syndrome (54.4%). In cases not associated with chromosomal anomalies, 82% were isolated malformations. Outcomes of pregnancies in cases with isolated malformations were a live birth in 88.1%, a TOPFA in 10.8%, and a fetal loss in 1.1% of cases. TOPFA and fetal loss were more frequent in cases with multiple malformations (33.1% and 3.1% respectively). For cases with chromosomal anomalies, pregnancy outcomes were: live birth in 20.5%, TOPFA in 77.1 fetal loss in 2.4%. 1062 cases (6.7%) were excluded from the calculation of the detection rate because they were related to other modalities of detection than ultrasound (mostly the first trimester combined test, less frequently another biological test or a systematic invasive test).

The overall prenatal detection rate (including cases with and without chromosomal anomalies) of ultrasound screening in the study period was 57.0%, ranging from 53.9% to 58.7% (Table 1). Consequently, 43% of cases were detected postnataly. The detection rate was substantially higher for cases associated with chromosomal anomalies, with a mean value of 91.2% [range: 88.4% - 93.2%]., The detection rate for cases without chromosomal

anomalies ranged from 48.2% to 53.4%, and was higher in cases of multiple anomalies (70.4%), than in cases with an isolated anomaly (47.8%). The logistic regression found a decreasing trend for the overall prenatal detection rate during the study period (OR=0,985; 95%IC: [0,972; 0,997]; p=0.015). Figure 1 represent this trend using moving averages (two-year period).

Resources leveraged for the ultrasound screening for fetal anomalies

In the 1/97 sample of the national claims database, we identified between 5,888 and 6,882 deliveries per year (0.7% to 0.8% of the total national number of deliveries). The mean maternal age in our sample was similar to the age observed in the national database (source: INSEE[16]). In 2014, an average of 4.08 US examinations were performed per pregnancy, for screening and other indications, compared to 3.78 in 2010. Table 2 shows the trend in the number of US examinations for the screening of fetal anomalies per pregnancy only. Between 2006 and 2014; we found an increase from 2.47 to 2.98 per pregnancy (+20.6%; p=0.005). We observed an increase of all types of US examinations, especially for the surveillance of fetal anomalies, which went up almost three fold during this period. The number of US examinations unrelated to the screening of fetal anomalies increased from 0.90 to 1.10 per pregnancy between 2010 and 2014, with an increase of 18% for dating ultrasounds and of 26% of US examinations performed for fetal growth surveillance. The average number of invasive procedures related to the US screening was stable during the study period, with an incidence of 0.015 per pregnancy.

We analyzed the trends for three subgroups defined by the number of scans performed per pregnancy: ≥4, 3 or ≤2. The trend in each subgroup is presented in figure 2. The percentage of women with ≥4 US examinations increased between 2010 and 2014 (+4.6%)

while those monitored according to the guidelines, i.e. three US examinations, decreased by 6%. Moreover, the proportion of women with fewer than three examinations than recommended by the guidelines remained stable.

Discussion

Using population-based data in France, we found that the average number of ultrasound examinations for the detection of fetal anomalies increased over the period 2006 and 2014, whereas the proportion of cases that were prenatally detected did not. The average number of scans increased from 2.47 to 2.98 per pregnancy during the study period whereas the overall proportion of fetal anomalies detected prenatally was approximately 60% and remained essentially stable over time diagnosed. These results suggest that that the increase in the use of resources for prenatal detection of congenital anomalies by ultrasound was not matched by increase in the proportion of congenital anomalies that were prenatally detected by ultrasound.

Our findings do not preclude that the proportion of cases that were prenatally diagnosed for some specific anomalies might have increased over time. However, given the essentially constant overall proportion of cases that were prenatally diagnosed, any such improvements must have been restricted to a limited number of anomalies and would have been relatively small in magnitude.

The 60% detection rate pertained to ultrasound only. Consequently, cases detected by other modalities were not taken into account (mostly the first trimester combined test with

NT < 99th), representing additional 7% of cases each year. Therefore, the global detection rate including all modalities of prenatal detection is expected to be slightly higher. Ultrasound screening is highly effective detecting malformations associated with chromosomal anomalies, with an average detection rate of 90.8%. Two-thirds of these cases were detected at first trimester US examination. This is of importance, because in these cases, most of the patients opt for TOPFA, which in return reduces the maternal morbidity when performed in earlier stage of pregnancy.

The stability of the detection rate of fetal anomalies that we observed contrasts with the continuous increase (+20.6%) of the number of US examinations performed between 2006 and 2014. This increase did not benefit to all women. Indeed, it occurred almost only in the sub group of women benefiting of four or more US examinations per pregnancy. This observation corresponds the results of the French National Perinatal Survey, which reported an increase in the average number of US examinations performed per pregnancy from 4.0 in 1995 to 5.0 in 2010 and 5.5 in 2016 (+10%)[17]. Similarly, we observed an increase of 8.2% between 2010 and 2014, considering all categories of US examinations. Additionally, in the French National Perinatal Survey, the proportion of women on whom more than 6 US examinations were performed during their pregnancy increased from 15.8% in 1995 to 35.9% in 2016. In parallel, the proportion of pregnant women with 3 US examinations decreased from 40.4% in 2003 to 24.3% in 2016. This survey is based on self-reporting data which makes it almost impossible to know what kind of US examinations was performed. In our study, the database only contained codes used by care providers to record US examinations, but no other clinical information or the precise indications for these examinations.

Previous studies have reported the trends in the prenatal detection rate of fetal anomalies with slightly different detection rates on specific abnormalities among European regions enrolled in the EUROCAT network[18–24]. One of our strengths is that we combined data from different registries to estimate the global prenatal detection rate in France. Additionally, our study focused on the contribution of US alone whereas other studies usually include all the modalities of detection of fetal anomalies, which makes it difficult to identify the contribution of US as the specific screening for aneuploidies is in constant evolution (from sequential to combined test to non-invasive testing using cell free DNA in the maternal plasma).

Our study had limitations and caveats. One is related to the lack of exact correspondence between the study population used for identifying trends in resource use (number of US examinations) vs. the study population for assessing trends in effectiveness of prenatal detection (proportion of cases prenatally detected). It is possible that the trends in resource use might be different for the subsample of the French population that resided in the catchment areas of the three registries. However, we have neither a priori reasons nor empirical evidence to suggest that this should be the case. Moreover, the prenatal diagnosis practices and policies are mainly decided at the national level. Hence, we do not believe that this lack of exact correspondence between our study populations for assessing trends in resource use vs. effectiveness could have biased our results in one way or another.

Due to a modification in the calculation of the hospital's funding between 2006 and 2009, the number of US examinations performed during this period in public hospitals was not recorded and had to be estimated. However, we have no reason to think there were differences between private and public providers during this period. In addition, public

hospitals account for less than 20% of US examinations, thus limiting a potential bias resulting from the estimation we have made for this period.

The development of US screening and its wide-spread use in France during the eighties led to a significant improvement of the prenatal detection rate of fetal anomalies. However, stagnation was observed from 2000s[25]. Our results confirm that stagnation in the detection rate. In parallel, we observed a significant increase of the number of US examinations performed. In addition, we observed that this increase did not benefit all the women. Conversely, the increase was even more pronounced in the sub group of women receiving more than recommended. The ecological design of our study limits the interpretation of the observed trends. However, the trend indicated a further increase in inequality of care for the surveillance of pregnant women. Although these results cannot be easily mapped to other countries, this study should stimulate similar analyses in other countries where a systematic screening of fetal anomalies using ultrasound is organized.

Conclusion

Our study has shown that even though the number of ultrasound examinations per pregnancy increased over time, the prenatal detection rate of fetal anomalies has not increased in recent years. These data suggest that there is a need to implement policies to improve the efficacy of ultrasound examination for prenatal diagnosis of congenital anomalies, including more high-quality training programs.

Tables and figures

Table 1. Fetal malformation detection rate between 2006 and 2014 by ultrasound screening. P-values for b-logit tests of the detection rate by year.

Table 2. Number of screening ultrasound examination per pregnancy between 2006 and 2014. (T1: first trimester, T2: second trimester, T3: third trimester). P-values for simple linear regression of the number of procedures per pregnancy by year.

Figure 1. Evolution of the overall ultrasound prenatal detection rate of birth defects during the study period using moving averages (two-year period).

Figure 2. Proportion of screening ultrasound examinations performed during pregnancy in three subgroups. Group A: 3 *ultrasound* examinations (thin line), Group B: 2 or less ultrasound examinations (bold line) and Group C: 4 or more ultrasound examinations (dotted line).

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Contributorship statement

All authors listed for this manuscript fulfill the ICMJE criteria.

CF, BK, JMJ and IDZ conceptualized the study and designed the analysis. FD was certified for the EGB database access. CF, FD, BK, LG, HR and IP collected the data. All authors contributed to perform the analysis. CF, FD, BK, JMJ, LG and IDZ wrote the final manuscript. JMJ and IDZ were the guarantor of the study.

Competing interest statement

Authors declare *no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.*

Funding statement

No funds were raised for this study.

Transparency statement

Authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Data sharing statement, details of ethics approval

There is no unpublished data.

It was a time-trend observation on aggregated data, provided by an analysis on anonymised individual data, and didn't require ethical approve. The EGB analysis, part of the SNIIRAM and property of the CNAMTS, was performed after INSERM approval and is covered by the *Commission Nationale de l'Informatique et des Libertés (CNIL*) (accords CNIL AT/CPZ/SVT/JB/DP/CR05222O du 14/06/2005 et DP/CR071761 du 28/08/2007).

Patient and public involvement statement

There was no patient nor public involvement in the design of the study.

References

1. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008 Jan 11;57(1):1–5.

2. Lee K, Khoshnood B, Chen L, Wall SN, Cromie WJ, Mittendorf RL. Infant mortality from congenital malformations in the United States, 1970-1997. Obstet Gynecol. 2001 Oct;98(4):620–7.

3. Hatton F, Bouvier-Colle MH, Blondel B, Pequignot F, Letoullec A. [Trends in infant mortality in France: frequency and causes from 1950 to 1997]. Arch Pediatr Organe Off Soc Francaise Pediatr. 2000 May;7(5):489–500.

4. Matthews TJ, MacDorman MF, Thoma ME. Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set. Natl Vital Stat Rep Cent Dis Control Prev Natl Cent Health Stat Natl Vital Stat Syst. 2015 Aug 6;64(9):1–30.

5. Sureau C, Henrion R. Assessment by the national committee for ulstrasound prenatal screening CNTE (Comité National Technique de l'Echographie de dépistage prénatal) report. 2005.

6. French Law: bylaw establishing guidelines for prenatal screening and diagnosis. Legislation : Arrêté du 23 juin 2009 fixant les règles de bonnes pratiques en matière de dépistage et de diagnostic prénatals avec utilisation des marqueurs sériques maternels de la trisomie 21. Source: internet. Avalable on <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000020814373, le 03/09/2017>.

7. French Law: law on organ donation, medically assisted procreation and prenatal diagnosisi Legislation : LOI no 94-654 du 29 juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal. Source : internet. Avalable on <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000549618&categorieLien=id>.

8. French Law: law on terminataion of pregnancy for medical reasons Legislation : LOI no 2001-588 du 4 juillet 2001 relative à l'interruption volontaire de grossesse et à la contraception. Source: internet. Avalable on <http://admi.net/jo/20010707/MESX0000140L.html le 03/09/2017>.

9. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017 Oct;65 Suppl 4:S149–67.

10. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954–62.

11. Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. Paper 1: The EUROCAT network--organization and processes. Birt Defects Res A Clin Mol Teratol. 2011 Mar;91 Suppl 1:S2-15.

12. EUROCAT guide 1.4, section 3.2. Minor anomalies for exclusion. Source: internet. Date: 11/11/2017. Link: http://www.eurocat-network.eu/content/Section%203.2-%2027_Oct2016.pdf.

13. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. BMJ. 1992 Apr 4;304(6831):867–9.

14. Taipale P, Hiilesmaa V, Salonen R, Ylöstalo P. Increased nuchal translucency as a marker for fetal chromosomal defects. N Engl J Med. 1997 Dec 4;337(23):1654–8.

15. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet Lond Engl. 1998 Aug 1;352(9125):343–6.

16. INSEE, average age of mothers at birth. Source: internet. Date: 11/11/2017. Link: https://www.insee.fr/fr/statistiques/2381390#tableau-Donnes.

17. Blondel B, Coulm B, Bonnet C, Goffinet F, Le Ray C, National Coordination Group of the National Perinatal Surveys. Trends in perinatal health in metropolitan France from 1995 to 2016: Results from the French National Perinatal Surveys. J Gynecol Obstet Hum Reprod. 2017 Oct 11;

18. Garne E, Loane M, Dolk H, De Vigan C, Scarano G, Tucker D, et al. Prenatal diagnosis of severe structural congenital malformations in Europe. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2005 Jan;25(1):6–11.

19. Garne E, Loane M, Wellesley D, Barisic I, Eurocat Working Group. Congenital hydronephrosis: prenatal diagnosis and epidemiology in Europe. J Pediatr Urol. 2009 Feb;5(1):47–52.

20. Boyd PA, Devigan C, Khoshnood B, Loane M, Garne E, Dolk H, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG Int J Obstet Gynaecol. 2008 May;115(6):689–96.

21. Pedersen RN, Calzolari E, Husby S, Garne E, EUROCAT Working group. Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. Arch Dis Child. 2012 Mar;97(3):227–32.

22. Garne E, Eurocat Working Group. Prenatal diagnosis of six major cardiac malformations in Europe--a population based study. Acta Obstet Gynecol Scand. 2001 Mar;80(3):224–8.

23. Boyd PA, Loane M, Garne E, Khoshnood B, Dolk H, EUROCAT working group. Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. Eur J Hum Genet EJHG. 2011 Feb;19(2):231–4.

24. Khoshnood B, De Vigan C, Vodovar V, Goujard J, Goffinet F. A population-based evaluation of the impact of antenatal screening for Down's syndrome in France, 1981-2000. BJOG Int J Obstet Gynaecol. 2004 May;111(5):485–90.

25. Khoshnood B, Lelong N, Lecourbe A, Ballon M, Goffinet F. Registre des malformations congénitales de Paris. Surveillance épidémiologique et diagnostic prénatal des malformations : évolution sur 35 ans (1981-2014). 2014.

Tables

Table 1. Fetal malformation detection rate between 2006 and 2014 by ultrasound screening. P-values for b-logit tests of the detection rate by year.

	Overall detection rate	Detection rate for cases without chromosomal abnormalities	Detection rate for cases with chromosomal abnormalities
2006	58.2%	52.2%	91.3%
2007	57.9%	52.3%	90.9%
2008	58.7%	52.6%	93.2%
2009	57.2%	51.9%	88.4%
2010	57.2%	52.4%	92.3%
2011	57.8%	53.4%	90.5%
2012	53.9%	48.2%	90.2%
2013	57.3%	52.8%	93.2%
2014	55.2%	50.2%	90.9%
p-value	0.015	0.170	0.975

Table 2. Number of screening ultrasound examinations per pregnancy, between 2006 and 2014. (T1: first trimester, T2: second trimester, T3: third trimester). P-values for simple linear regression of the number of procedures per pregnancy by year.

Procedures	2006	2007	2008	2009	2010	2011	2012	2013	2014	p-value
T1 Ultrasound	0,73	0,79	0,92	0,88	0,89	0,89	0,87	0,88	0,88	0,102
T2 Ultrasound	0,84	0,80	0,96	0,92	0,94	0,95	0,94	0,95	0,95	0,033
T3 Ultrasound	0,82	0,74	0,89	0,85	0,88	0,87	0,87	0,89	0,87	0,102
Surveillance	0,07	0,11	0,11	0,13	0,14	0,17	0,18	0,24	0,26	0,003
Fetal Heart	0,01	0,02	0,01	0,02	0,02	0,02	0,02	0,02	0,03	<0,001
Total	**2,47**	**2,45**	**2,89**	**2,79**	**2,87**	**2,90**	**2,89**	**2,98**	**2,98**	**0,005**

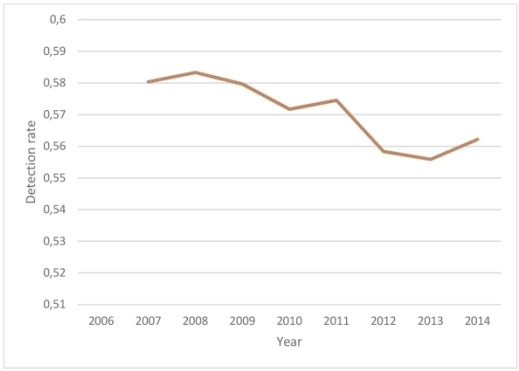

figure 1

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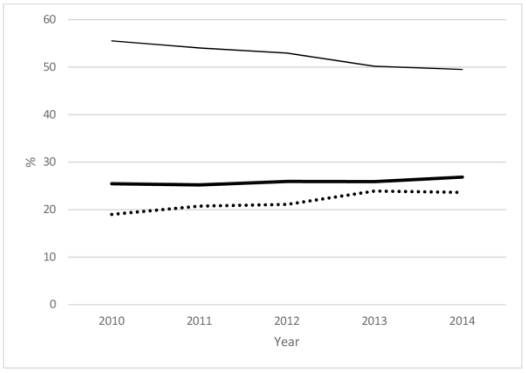

Figure 2. Proportion of screening ultrasound examinations performed during pregnancy in three subgroups. Group A: 3 ultrasound examinations (thin line), Group B: 2 or less ultrasound examinations (bold line) and Group C: 4 or more ultrasound examinations (dotted line).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	X
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-9
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	X
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	X
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*X*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*X*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8-9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.