Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Implementation of PAPP-A as a screening test for stillbirth by NHS England.		
Period when the underpinning research was undertaken: April 2002 to Nov 2004		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Professor Gordon CS Smith	Professor of Obstetrics & Gynaecology	1st September 2001 to present
Period when the claimed impact occurred:2014 to present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Stillbirth is the major cause of baby death, with an estimated 1,700,000 cases worldwide in 2016. In 2011, the UK had the 3rd highest stillbirth rate of 35 high income countries. Cambridge research first showed that low maternal blood levels of Pregnancy Associated Plasma Protein A (PAPP-A) in early pregnancy were associated with an increased risk of stillbirth due to foetal growth restriction (FGR). As a direct consequence, NHS England recommended that women with low PAPP-A in early pregnancy undergo enhanced ultrasonic surveillance. Implementation of this policy has been associated with a 60% increase in detection rate of FGR and subsequent intervention prevents >500 fewer stillbirths per annum in England.

2. Underpinning research (indicative maximum 500 words)

It is widely recognised that poor foetal growth is one of the major risk factors for stillbirth. In the 20th Century, efforts to identify causes of FGR focused on the second half of pregnancy, since it was widely believed that foetal growth in early pregnancy is determined genetically. However, a seminal paper by Smith (Smith et al., NEJM 1998) first showed that foetal growth in the first trimester is significantly associated with the risk of delivering a low birth weight baby at term; suggesting that environmental variables during early pregnancy are important determinants of FGR. In his 1998 NEJM paper Smith hypothesised that this might involve placental dysfunction.

Maternal serum PAPP-A as a test of early placental function: To test this hypothesis, Smith measured maternal serum levels of PAPP-A in early pregnancy and correlated this with subsequent pregnancy outcome. PAPP-A is produced by the placenta to critically regulate Insulin Growth Factor 2 (IGF2), a key regulator of placental growth. Low PAPP-A would be expected to be associated with low IGF2, limiting placental growth and thereby predicting stillbirth and low birth weight. Working together with a team studying new methods of screening for Down's syndrome (CUBS study), Smith led research that looked at maternal serum levels of PAPP-A between 10 and 14 weeks of pregnancy in almost 9,000 women. These data showed for the first time that low first trimester levels of PAPP-A are significantly associated with increased stillbirth risk [1]. This research further showed that low PAPP-A levels are associated with the risk of delivering a low birth weight infant at term, confirming a link between PAPP-A and FGR [2].

Deploying PAPP-A to prevent stillbirth through enhanced surveillance: To enable effective translation of PAPP-A to the clinic, it was critical to define if low PAPP-A levels are directly associated with stillbirth caused by FGR. This was a key question, since, if low PAPP-A and stillbirth were related for reasons other than FGR, it could not be assumed that enhanced subsequent surveillance of the pregnancy with ultrasound would mitigate the risk. To address this question Smith used record linkage of the CUBS study dataset to routinely collected data from NHS Scotland. With the approval of the Privacy Advisory Committee of the NHS Scotland Information Services Division, Smith led a research team that linked the CUBS dataset to the Scottish Stillbirth and Infant Death Enquiry, a national register of stillbirth and neonatal deaths. Analysis of this new dataset allowed the level of PAPP-A to be related to stillbirths attributed to different causes. This study showed that the relationship between low first trimester PAPP-A and stillbirth was wholly explained by an association with stillbirth secondary to placental dysfunction in general, including FGR [3]. This finding provided the rationale for serial scanning of women in late pregnancy who had low PAPP-A in early pregnancy to prevent stillbirth. Ultrasound is used in pregnancy to plot the growth of the foetus, to identify growth restriction, and to assess the pattern

of blood flow to the placenta (umbilical artery Doppler flow velocimetry), to identify placental insufficiency. Identifying the types of stillbirth associated with low PAPP-A provided a rationale that later ultrasonic surveillance could identify the babies at risk of stillbirth, allowing their early delivery before intra-uterine death occurred. This work also inspired a series of studies that were subsequently reviewed systematically, confirming the association between low first trimester PAPP-A and stillbirth (Conde-Agudelo et al, *BJOG* 2015).

3. References to the research (indicative maximum of six references)

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1] ***Smith GCS**, … Connor JM. Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intra-uterine growth restriction, premature birth, pre-eclampsia and stillbirth. Journal of Clinical Endocrinology and Metabolism 2002;87:1762-7.

A PubMed search using the terms "PAPP-A AND stillbirth" yields >50 citations and citation #1 is the JCEM paper.

[2] ***Smith GCS**, … Connor JM. Early pregnancy origins of low birth weight. Nature 2002;417:916.

[3] ***Smith GCS,** …Dobbie R. First trimester placentation and the risk of antepartum stillbirth. JAMA 2004; 292:2249-2254. *

Competitive funding received

The Chief Scientist's Office of the Scottish NHS Executive and the Fetal Medicine Foundation

4. Details of the impact (indicative maximum 750 words)

Each year, around 3,000 babies are lost to stillbirth in the UK. More than 90% do not have a congenital anomaly and more than three quarters occur at 28 weeks of gestational age or beyond, when survival is the norm if a baby is delivered. Hence, on the basis of lack of an anomaly and viable gestational age, more than half of the losses are potentially preventable by medically-indicated delivery if the baby had been known to be at risk of stillbirth. Prior to August 2013, Smith made substantial contributions to raising the public profile of stillbirth as a problem in the UK; in particular, a series of high-profile papers in the Lancet including Smith's 2007 Seminar on Stillbirth, and the 2011 Lancet Stillbirth Series to which Smith contributed significantly. The latter demonstrated that the UK had the 3rd highest stillbirth rate out of 35 high income countries. Smith also featured heavily in a 2014 BBC Panorama documentary of stillbirth ("Born Asleep") [A]. In July 2015, in response to Smith's review in *The Obstetrician & Gynaecologist* calling for better monitoring of women during their pregnancy to prevent stillbirth, stillbirth & neonatal death charity (Sands) released a press release that "*welcomes Professor Smith's clear overview and critique of recent developments in stillbirth prevention*" and called for better monitoring to prevent stillbirth [B].

Impact on public policy

The increasing profile of stillbirth as an issue and the UK's poor record in this area led to action from the UK government. The Health Secretary, Jeremy Hunt, announced on 13 November 2015 an ambition to reduce stillbirth rates by 50% by 2030. Reducing stillbirths was also included in the NHS Outcomes Framework and was included in the NHS England Business Plan for 2015-16. The Government's mandate to NHS England 2016-17 (section 2.1) requires "*measurable progress towards reducing the rate of stillbirths, neonatal and maternal deaths and brain injuries that are caused during or soon after birth by 50% by 2030 with a measurable reduction by 2020*." [C].

Impact on practitioners and the delivery of professional services

This political ambition led NHS England to produce a care bundle aimed at reducing stillbirth rates articulated in "Saving Babies' Lives" published on 21 March 2016 [D]. The target audience was all staff delivering maternity care as well as Clinical Commissioning Group Clinical Leaders, Medical Directors, Directors of Nursing and Allied Health Professionals. The care bundle was supported by key stakeholders, such as the Royal College of Obstetricians and Gynaecologists and the Royal College of Midwives, as well as charities representing consumers. The bundle included the recommendation that all women with a low level of PAPP-A in early pregnancy should have serial

ultrasound scans from 26-28 weeks, including umbilical artery Doppler, until delivery and this is recommended to reduce the risk of stillbirth. As discussed above, ultrasound can be used to detect FGR and placental insufficiency, hence the demonstration that the association between low PAPP-A and stillbirth was due to these causes was key to informing the subsequent use of serial ultrasound in these women. There is level 1 evidence that use of umbilical artery Doppler in high risk pregnancies reduces the risk of perinatal death (stillbirth or early neonatal death) (Alfirevic Z et al, Cochrane Database Syst Rev2017).

Impact on the health and wellbeing of people

The beneficiaries were pregnant women, their families, health care professionals and the NHS in England. In May 2016 NHS England commissioned the Tommy's Stillbirth Research Centre at the University of Manchester to evaluate the impact of the Saving Babies Lives care bundle on stillbirth rates. The result was the "Saving Babies Lives Project Impact and Results Evaluation (SPiRE) study (www.clinicaltrials.gov NCT03231007) [E]. The SPiRE study report (published in July 2018) concluded "*During the time period analysed in the early adopter Trusts there was a statistically significant reduction in stillbirth of 20%; this reduction was also seen in term stillbirths. Due to variations in the timing and level of implementation of the various elements of the care bundle this reduction cannot be unambiguously related to its implementation. However, it is highly plausible that the care bundle contributed to the fall in stillbirths*." [F]

As the report states, it is impossible to prove that the Care Bundle was responsible for the fall in stillbirth rates but the report does state that it is "highly plausible". Moreover, it is impossible to separate out the individual contributions of different elements of the Care Bundle to the fall in stillbirths. However, approximately 90% of Trusts implemented the risk assessment tool, which included serial scanning of women with low early pregnancy PAPP-A, either fully or partially. Moreover, the SPiRE study reported that antenatal detection of small babies increased by approximately 60% over the period of implementation, which was associated with a 31% increase in the use of serial ultrasound. The rate of induction of labour, the primary method for preventing stillbirth of the high-risk foetus, also increased from 26.3% to 31.4%. Hence, it is also highly plausible that implementation of serial scanning to assess foetal growth in women with a low PAPP-A increased detection of small babies and prevented stillbirths.

NHS England produced version 2 of the Saving Babies' Lives Care Bundle in 2019 and it continues to recommend serial ultrasonic surveillance of women with low first trimester PAPP-A. [G]. Smith was one of seven experts who oversaw the development of the care bundle and was one of only two experts who was on the contributory panels of all five elements of the care bundle.

International impact

Smith's work on stillbirth prediction is recognised internationally, for example, through the International Stillbirth Alliance Distinguished Researcher Award (presented in Sydney, Australia, 2010). In relation to PAPP-A, although the evidence for impact is strongest in the UK, using low PAPP-A to guide the assessment of risk of stillbirth in pregnant women is also described in international guidelines, from bodies including the New Zealand Maternal Fetal Medicine Network ('Low PAPP-A is associated with increased risks of SGA [Small for gestational age]') [H], the South Australian Maternal & Neonatal Community of Practice ("Women who have a low PAPP A on 1st trimester screening should be counselled by the medical practitioner ordering the test about the risk of complications of pregnancy associated with low PAPP-A") [I], the Government of the State of Queensland, Australia (low PAPP-A at the time of first trimester screen is listed as a risk factor to take into consideration for stillbirth) [J].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] BBC Panorama documentary of stillbirth. https://www.bbc.co.uk/programmes/b04kmppc
[B] The Government's mandate to NHS England for 2016-17, pp. 12-13.
[C] Sands response to GS's review calling for better monitoring to prevent stillbirth.
[D] First iteration of the NHS England SBL Care Bundle: O'Connor D. *Saving Babies' Lives A care bundle for reducing stillbirth* report for NHS England. 21 March 2016, p19.

[E] Description of the study analysing the effect of implementation of NHS England SBL Care Bundle: Tommy's Stillbirth Research Centre, the University of Manchester, Saving Babies Lives Project Impact and Results Evaluation (SPiRE) study

[F] Analysis of the effect of implementation of NHS England SBL Care Bundle: Widdows K, Roberts SA, Camacho EM, Heazell AEP. *Evaluation of the implementation of the Saving Babies' Lives Care Bundle in early adopter NHS Trusts in England*. Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK. 2018, p9.

[G] Second iteration of the NHS England SBL Care Bundle: NHS England. *Saving Babies' Lives Version Two A care bundle for reducing perinatal mortality* report. March 2019, p56.

[H] Report demonstrating awareness of PAPP-A as a risk factor for stillbirth in New Zealand: McCowan L, Bloomfield F, Parry E, Groom K and Necas M. *Guideline for the Management of Suspected Small for Gestational Age Singleton Pregnancies and Infants After 34 Weeks' Gestation* report for the New Zealand Maternal Fetal Medicine Network (NZMFMN). 2013, updated 2014, p7.

[I] Report demonstrating awareness of PAPP-A as a risk factor for stillbirth in South Australia: SA Maternal & Neonatal Community of Practice. *Management of Women with a Low PAPP-A and Normal Chromosomes* policy guideline for South Australian Perinatal Practice Guidelines (SAPPG). 19 April 2016, p6.

[J] Report demonstrating awareness of PAPP-A as a risk factor for stillbirth in Queensland, Australia: Queensland Clinical Guidelines team. *Stillbirth Care* guideline for Queensland Clinical Guidelines Steering Committee and Statewide Maternity and Neonatal Clinical Network (Queensland). Updated March 2019, p9.