Female childhood cancer survivors and the impact of flank, abdominal or pelvic radiotherapy on live birth rates: A systematic review and meta-analysis

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Abstract

Population:

Adult female survivors of childhood, adolescent, and young adult cancers (Childhood cancer survivors (CCS) have a survival rate of up to 84%, with many now able to maintain fertility into adulthood.

Intervention:

This review critically appraised and synthesised evidence for live birth rates and adverse pregnancy outcomes of female CCS (aged 0-24 at diagnosis), treated with radiotherapy to the abdomen, flank, or pelvis. MEDLINE, PUBMED, CINAHL, Google Scholar, TRIP, SCOPUS, and ProQuest were searched on 30th of September 2017 and on the 11th of June 2020. Studies were subjected to inclusion and exclusion criteria with secondary independent review. Public and Patient Involvement and Engagement (PPIE) was used to assist in the selection of outcomes.

Data were analysed using *EPPI Reviewer 4.* Risk of bias was assessed using The Newcastle Ottawa scale (NOS). Meta-analysis used a random effects model (Der-Simonian and Laird) with parameters of heterogeneity set at I^2 of > 50% and a chi-squared p value of <0.05 using *RevMan 5* software. The review adhered to PRISMA (2009) reporting guidelines and flow chart.

Comparator:

Sibling control groups and/or general population controls with no history of treatment for childhood cancer where available.

Outcomes:

The database search yielded 1495 studies; 1289 screened for title and abstract; 26 screened as full text, eight used for meta-analysis. Upon aggregation (11th of June 2020), one study was added and used in the meta-analysis (total n=9 used for meta-analysis).

Female CCS who received radiotherapy to the flank, abdomen or pelvis had an increased odds of premature birth (<37 weeks gestation) (OR 3.69 CI [2.82, 4.81] p= < 0.00001) and miscarriage (OR 1.59 CI [1.37, 1.84] p=< 0.00001), when compared to CCS that had not had radiotherapy. CCS exposed to radiotherapy had increased odds of stillbirth (OR 1.72 [1.08, 2.74] p= 0.02) when compared to non-CCS controls. Data for live birth rates were not analysed due to heterogeneity and control group variance.

Female CCS warrant high-risk antenatal care and ongoing surveillance throughout pregnancy. Further research investigating toxic thresholds of the uterus is recommended. Female CCS require detailed communication of future pregnancy risk before pregnancy occurs.

Trial registration:

The protocol was registered with PROSPERO (CRD42017054533) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=54533)

Keywords:

Childhood cancer survivor, adult cancer survivor, childhood neoplasms, survivorship, pregnancy, birth, live birth, adverse outcome, radiotherapy, evidence-based midwifery

Word count:

Abstract – 349, Abstract + Whole article - 4919

Background

The survival rate for children, adolescents and young adults with cancer is approximately 84 percent at five years following diagnosis (Cancer Research UK, 2021). However, cancer treatments given to a child are known to cause significant long-term, chronic health problems in adulthood (Children's Cancer and Leukaemia Group, 2021). Many female childhood cancer survivors (CCS) now maintain their fertility and can go onto conceive a natural pregnancy (van de Loo et al 2019, van der Kooi et al 2019). The number of CCS in the United Kingdom (UK) is currently estimated to be around 35,000 (Cancer Research UK, 2021) and rising. Therefore, it is important to consider long-term health outcomes of CCS, including reproductive outcomes for future pregnancy and birth. Risk of adverse outcome linked to prior cancer treatments merits further investigation with a need to increase awareness of health care professionals, female CCS, and their families about potential risks (van de Loo et al 2019, van der Kooi et al 2019).

Treatment for childhood cancer often requires a combination of chemotherapy, radiotherapy, surgery, and immunotherapy treatments (Children's Cancer and Leukaemia Group, 2021). The use of radiotherapy to the flank, abdomen or pelvic areas is dependent on the site, stage, and type of tumour (Children's Cancer and Leukaemia Group, 2021). Tumours that often require radiotherapy to the flank, abdomen or pelvis include Wilms tumour, neuroblastoma, leukaemia (when total body irradiation is used), Hodgkin's lymphoma, rhabdomyosarcoma, and germ cell tumours (Children's Cancer and Leukaemia Group, 2021). Radiotherapy delivered to the uterine area in a child that has yet to reach puberty, has been reported to increase the likelihood of abnormal organ development and growth; resulting in an inability to carry a pregnancy to full term (van der Kooi et al 2021, van de Loo et al 2019, Larsen et al 2003). This increases the likelihood of adverse pregnancy and birth outcomes, such as pre-term birth (<37 weeks gestation) (van de Loo et al 2019, van der Kooi et al 2019).

The pre-menarche uterus has been reported to be progressively radio-sensitive, which increases the risk of abnormal development in adolescence (Larsen et al

2003). Furthermore, Van de Loo et al (2019) reported that female CCS treated with radiotherapy to the abdomen had lower uterine volumes than general population controls and a higher risk of premature labour. Additional radiotherapy-induced malformations of the uterus have been reported as abnormal placental formation, abnormal conversion of uterine spiral and distal arteries, and abnormal placentation (placenta praevia, percreta or accreta) (Lie Fong et al 2010). Female CSS treated with radiotherapy to the abdominal area were also found to be at risk of uterine rupture and cervical insufficiency (Lie Fong et al 2010, Reulen et al 2009). Research to determine the causal link between level of radiotherapy treatment received and risk of adverse outcomes in pregnancy and birth for female CCS is lacking (Reulen et al 2009).

The voice of the female CCS and their families within the design, prioritisation and dissemination of research in this area is also absent. This systematic review highlights the need for embedded public and patient involvement and engagement (PPIE) in CCS research. Likewise, the ability to use PPIE within a systematic review design has been demonstrated by this review, illustrating how PPIE can be embedded into any type of research. To achieve this, data were collected from female CCS and their parents using an online survey to determine patient/parent research priorities for the area of future treatment-related pregnancy risks. Data obtained from the online surveys were compared to the selected primary and secondary outcomes to ensure compatibility. This approach aimed to ensure that the focus of the review aligned with the patient-reported research priorities and needs.

The aim of the review was to evaluate, appraise and synthesise the existing data for live birth rates of female CCS who received flank, abdominal or pelvic radiotherapy as treatment for childhood cancer. The results aimed to provide health care professionals and female CCS with an additional evidence base when planning a pregnancy or accessing maternity services.

Methods

The PRISMA flow chart and reporting checklist were used to structure the systematic review and meta-analysis (Moher et al 2009). Ethical approval was gained from Coventry University Ethics Committee (P46688 and P60599) and the systematic review was registered with the PROSPERO (CRD42017054533). An extensive

bibliographic search was conducted, and risk of bias performed using the Newcastle Ottawa Scale (NOS) (Wells et al 2018). Meta-analysis of outcomes was undertaken if more than three reports with the same clinical outcome and population/comparators were found.

Review questions:

(1) What is the impact of flank, abdominal or pelvic radiotherapy given to female childhood/adolescent/young adult cancer survivors upon subsequent live birth outcomes?

(2) Are there any identified perinatal risks directly attributable to radiotherapy to the flank, abdomen, or pelvis as a child/adolescent/young adult?

Study selection criteria:

Inclusion criteria:

- Women who had given birth (aged >=16 years old)
- Women who received a diagnosis of cancer as a child or adolescent/young adult (up to age 24 years inclusive) who had flank, abdominal or pelvic radiotherapy as part of their treatment
- Naturally occurring pregnancy without fertility treatment (including in-vitro fertilisation (IVF)
- Pregnancy, not within one year of active cancer treatment

Sources were selected from recognised data registries, from the United States of America (USA), Australia, Canada, and other European Union (EU) member countries. Studies were cohort or case-controlled by design and published in English. Control or comparator groups were deemed eligible for data correlation/comparison if derived from non-cancer affected siblings/general population or non-radiotherapy exposed CCS.

Exclusion criteria:

- Male CCS
- Surrogate pregnancies of CCS
- Females treated for adult cancer >age 25 at diagnosis

- Females treated for cancer during pregnancy or pregnancies <1yr from end of treatment
- Pregnancies achieved using artificial reproductive techniques such as IVF
- Female CCS treated with radiotherapy to other area of the body or where treatment site or type were not able to be extrapolated from data
- Data that could not extrapolated to distinguish number of male/female CCS

These exclusion criteria were applied to ensure coherent and consistent analysis of variables in this particular field of research, i.e., health care systems and access to healthcare that were comparable to those in the United Kingdom.

Search approaches:

A search of MEDLINE, PubMed, CINAHL, Google Scholar, Scopus, TRIP and ProQuest databases was performed on the 30th of September 2017 with an aggregate review conducted on the 11th of June 2020. The databases were selected to ensure a wide representation of studies from the nursing, oncology, obstetric and psychological disciplines. The reference lists of included studies were scanned, forward cited and back-referenced. All titles and abstracts were scanned AP. Those not deemed ineligible were further assessed in full-text format. A selection of 10% of the titles/abstracts was screened by NA. This also applied to papers selected for full-text assessment. Conflicts in inclusion of studies to the review were not found. However, a third independent reviewer was available throughout the process to ensure methodological compliance. PRISMA reporting guidelines were followed and a modified Cochrane data extraction template used. Risk of bias and data extraction was checked by NA prior to meta-analysis.

Outcome selection:

An online pseudo-anonymised survey of 12 questions was completed by 26 female CCS (aged ≥16 years old) who had given birth to a child, and parents of female CCS survivors yet to conceive a child. Participants were asked to complete the short survey and rank importance of selected outcomes for the review. *Qualtrics* was used to design the survey and collect data. Participants for the PPIE survey were recruited via an invitation posted on CCS online support groups and social media platforms. The results of the survey were used to verify the selected primary and secondary outcomes of the review.

Outcomes:

Primary outcome:

- Live birth at term (37 weeks of completed pregnancy)

Secondary outcomes:

- Pregnancy Outcome (Live birth, miscarriage, stillbirth, neonatal death up to 28 days and intrauterine death), premature birth (24 weeks to 36+6 weeks gestation), fetal growth restriction (below 10th centile of predicted growth projection), Low birth weight (<2.5kgs at birth), caesarean section rate (elective or emergency), onset of labour type (spontaneous, induced or augmented), uterine dysfunction (defined as delayed first stage requiring syntocinon augmentation and postpartum haemorrhage) and neonatal congenital abnormality.

The protocol was registered with PROSPERO (CRD42017054533).

Data Analysis:

A Cochrane data extraction template was modified to enable collection of data including cancer type, treatment and dose, age at treatment, ethnic background, age at pregnancy and other adverse obstetric events. Raw binary data were extracted from the individual studies for outcomes by the first reviewer using a 2x2 contingency table. If raw data could not be found within the paper, then the authors were contacted to provide this information, with studies excluded for meta-analysis if no response received or data were unobtainable two weeks after the request.

Data synthesis:

Outcome measures from included studies were recorded, tabulated and meta-analysis subsequently considered. Narrative review was used for data from outcomes deemed too heterogeneous for meta-analysis and sub-group analysis was planned for, but not undertaken due to limitation of available studies and heterogeneity of studies. Meta-analysis was undertaken using the software *RevMan 5,* using a random effects model. This represented the belief that true effect size might differ from study to study due to variables in population demographics. An initial consideration of clinical homogeneity was undertaken to decide if an outcome

was matched in the data of at least three of the included studies (including control group data). If this was not apparent, then meta-analysis was not undertaken.

Risk of bias assessment:

This was assessed at the individual study level using the NOS Scale (Wells et al 2018) by AP and NA. Studies were categorised with the most robust studies (highly assessed and rigorous research) achieving up to nine stars. High quality studies were defined as those which had achieved a score of seven or more, based on similar NOS categorisations used in systematic reviews of this kind (Kabak et al 2019). Risk of bias across studies was not assessed due to methodological heterogeneity.

Results

PPIE survey:

The PPIE online survey was completed by 24 participants using *Qualtrics* software survey tool. The demographical background of the participants represented parents of children that have had cancer (19 out of 23) and three female CCS who had given birth. 16 participants recorded that they/their child had received radiotherapy to the 'tummy'. The three-top-ranking future pregnancy concerns were identified as:

1. Risk of pregnancy complications of the mother
2. Risk of miscarriage and abnormality in the baby
3. Risk of early labour

The outcome of 'live birth' was not directly asked, however the term 'A healthy baby' was included and ranked fourth in the survey.

Review results and meta-analysis:

The database search identified 1495 records, 26 were reviewed in full-text and 10 included in the final review. Following aggregate review on the 11th of June 2020, a further study was added to the final number (final number n=11 included and n=9 used for meta-analysis). Data from this study were added to the existing summary table and meta-analysis repeated to include the new data. Two studies were excluded for meta-analysis due to unavailability of raw data.

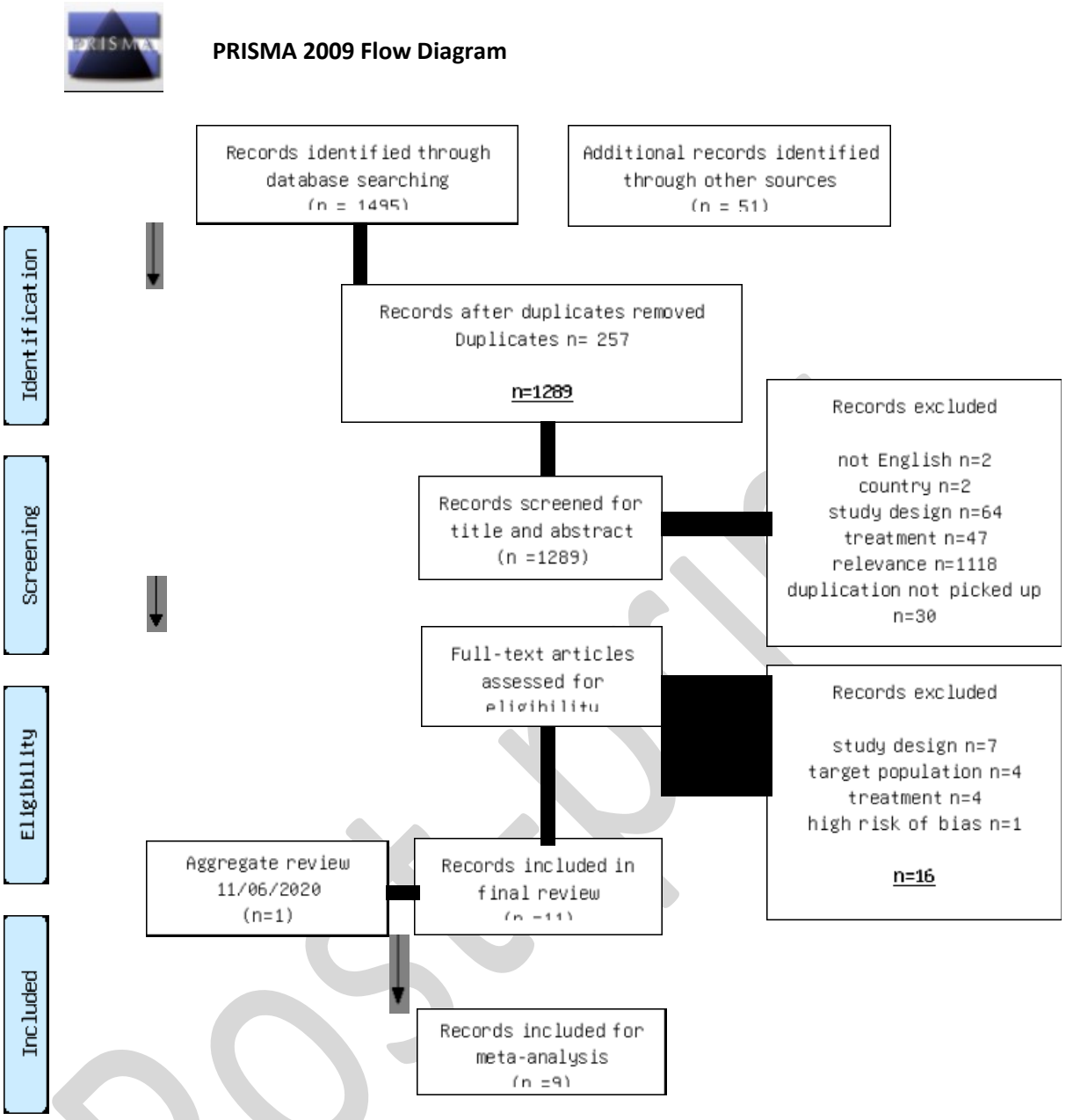


Figure 1 PRISMA 2009 Flow Diagram

The final included studies consisted of 11 retrospective cohort studies (Table 1). The studies represented recognised data registries including the British Childhood Cancer Survivor Study (BCCSS) (Hawkins et al 2008) and the Childhood Cancer Survivor Study (CCSS) (Robison et al 2002). Several of the studies used medical records to corroborate patient reported outcomes, however authors included missing treatment data where possible. The included studies varied in population size from less than 1000 to more than 34000. All included studies had one or more comparator control groups. Data were provided in three studies for two different categories of

control (non-CCS sibling and general population controls) (van de Loo et al 2019, Winther et al 2008, Green et al 2002). Sample sizes ranged from <1000-3000+ and included a variety of convenience, purposeful (sibling matches) and random (data linkage comparisons from data registry) sampling methods. Of the 11 included studies, five studies provided data for CCS exposed versus CCS non-exposed groups and eight studies provided data for the general population or sibling matches.

Table 1 Summary table of included studies

* Low birth Weight (<2500grams), ^ Premature birth <37 weeks gestation, ~ Small for Gestational age (<10th birth percentile), † all CCS vs siblings (not treatment specific), ‡ Premature rupture of membranes, § Gestational diabetes

Author	*Cases n=*	*Control n=*	*Comparator n=*	*Control/comparison background*	*Outcomes*	*Crude data Cases*	*Crude data Control*	*OR*	*RR*	*Main findings*
Green et al. 2002	4029	1903	1680	Siblings	**Sibling control**					• Overall no significant results in outcome by treatment • Higher risk of miscarriage for female CCS treated with ovarian radiotherapy • Female CCS treated with radiotherapy more likely to have LBW infant
				CCS exposed vs CCS non-exposed	Live birth	131/101	1349/554	0.53	0.79	
					Stillbirth	2/230	13/1890	1.26	1.26	
					Miscarriage	46/186	279/1624	1.43	1.35	
					LBW†	172/2376	36/1313	2.64	2.52	
					Abortion	39/193	220/1683	1.54	1.45	
					CCS exposed vs CCS non- exposed					
					Live birth	1472/877	1076/604	0.91	0.97	
					Miscarriage	463/1886	239/1441	1.48	1.38	
					Stillbirth	25/2326	14/1666	1.27	1.27	
					Abortion	460/1889	304/1376	1.1	1.08	
Green et al. 2010	312	0	187	CCS exposed vs CCS non-exposed	Live birth	312/187	187/312	2.78	1.66	• Increase in LBW and premature labour increased in female CCS who received radiotherapy
					Hypertension	74/425	23/476	3.6	3.21	

					Premature labour	79/420	28/471	3.16	2.82	• No trend found for risk of congenital abnormalities • Increased risk of hypertension, malposition of fetus for female CCS who received radiotherapy (increased with radiation dose)
					Malposition	31/468	8/491	4.06	3.87	
					Obstructed labour	23/476	12/487	1.96	1.91	
					Abnormality of force	18/481	14/485	1.29	1.28	
					Cord complications	77/422	36/463	2.34	2.13	
					Premature birth	62/437	19/480	3.58	3.26	
					PROM‡	11/488	11/488	1	1	
					Congenital abnormality	28/284	16/171	1.06	1.04	
Reulen et al.2017	2783	25000	0	General population	Hypertension (pre-existing and non)	101/2682	2508/22492	0.33	0.36	• 3-fold increase in hypertension found in female CCS who received radiotherapy • Increased risk of GDM and anaemia found for female CCS treated with radiotherapy • Female CCS more likely to have caesarean section
					Live birth (exposed CCS vs non-exposed CCS)	326/2457	860/1923	0.29	0.37	
					GDM§	16/2767	390/24610	0.36	0.36	
					Anaemia	27/2756	1099/23901	0.21	0.22	
					Growth issues	24/2759	1431/23569	0.14	0.15	
					Post-term pregnancy	18/2765	1349/23651	0.11	0.11	
					Labour complications	127/2656	10448/14552	0.06	0.10	
					PROM	21/2762	1913/23087	0.09	0.09	

					Mal-presentation	17/2766	1058/23942	0.13	0.14	
					Caesarean	122/2661	5423/19577	0.16	0.20	
					Haemorrhage	41/2742	2179/22821	0.15	0.16	
Lie Fong et al. 2010	40 (6 had RT)	9031	0	General population	Congenital abnormality	0/6	145/8834	4.67	4.40	• Pregnancy outcome not different for either group • Female CCS exposed to abdominal radiotherapy had more preterm babies and haemorrhage • Normal birthweight was found for babies of female CCS after adjustment for age at birth
					Pre-eclampsia	0/6	40/8991	17.07	15.92	
					Haemorrhage	2//4	449/8232	9.16	6.44	
					Manual removal	1//5	251/8430	6.71	5.76	
					Caesarean (emergency and elective)	0//6	1296/7735	0.45	0.49	
Signorello et al. 2006	1264 (2201 births)	601 (1175 births)	0	Siblings	Live birth†	2309/1220	1209/491	0.76	0.92	• Female CCS more likely to be premature birth • Female CCS treated with abdominal radiotherapy at increased risk of premature birth • Female CCS at increased risk of small for gestational age and LBW babies
					Livebirth (CCS exposed vs non-exposed)	1116/1085	617/558	0.93	0.96	
					Premature birth (RT uterus)	252/864	145/1007	2.02	1.79	
					Premature birth (RT ovary)	172/701	145/1007	1.7	1.56	
					Premature birth (cumulative)	424/1565	145/1007	1.88	1.69	
					Low birth weight (RT uterus)	106/1026	48/1094	2.35	2.22	
					Low birth weight (RT ovary)	65/814	48/1094	1.81	1.75	

					low birth weight (cumulative)	171/945	48/1094	2.11	3.64	
					Small for gestational age (cumulative) (ovary+ uterus RT)	159/1758	101/1002	0.89	0.90	
Reulen et al. 2009	509	0	1422	CCS exposed vs CCS non-exposed	Live birth	351/158	1048/374	0.79	0.93	• Female CCS treated with radiotherapy at increased risk of preterm birth and LBW and small increased risk of miscarriage • Live birth rate was 2/3 lower than expected for female CCS (particularly when exposed to abdominal radiotherapy)
					Miscarriage	96/413	209/1213	1.34	1.28	
					Stillbirth	3/506	7/1415	1.19	1.19	
					Premature delivery	90/419	95/1327	3	2.64	
					LBW	75/276	77/971	3.42	2.90	
					Termination	59/450	158/1264	1.04	1.04	
Signorello et al. 2010	1014	0	596	CCS exposed vs CCS non-exposed	Livebirth (all CCS vs exposed CCS)	3077/60	4853/93	0.98	0.99	• Female CCS exposed to abdominal radiotherapy at increased risk of stillbirth and neonatal death
					Stillbirth/ neonatal death	39/3098	21/3116	1.86	1.85	
Van der Loo et al. 2019	14	33	37	CCS exposed vs CCS non-exposed	**<u>CCS exposed vs CCS non-exposed</u>**					• CCS exposed were at increased risk of reduced uterine volume (<44.3ml) when compared to general population • CCS exposed had an increased risk of premature labour, pregnancy complications and low birth weight
				CCS exposed vs general population	Small uterus	4/10	12/21	0.70	0.78	
					Pregnancy complication	10/4	13/20	3.84	1.81	
					Miscarriage	4/10	7/26	1.48	1.34	
					Premature delivery^	6/8	9/24	2	1.57	

					LBW*	5/9	3/30	5.55	3.92	babies than general population
					SGA~	1/13	2/31	1.19	1.17	• CCS exposed had an increased risk of low birth weight babies than CCS non-exposed
					CCS exposed vs general population					• Uterine exposure to radiotherapy increases risk of pregnancy complications and adverse outcomes. Pre-conception counselling and obstetric monitoring recommended
					Small uterus	4/10	7/30	1.71	1.51	
					Pregnancy complication	10/4	8/29	9.0	3.30	
					Miscarriage	4/10	7/30	1.71	1.51	
					Premature delivery^	6/8	3/34	8.50	5.28	
					LBW*	5/9	1/36	20.0	13.21	
					SGA~	1/13	2/35	1.34	1.32	
Winther et al. 2008	1688	16700	2737 (siblings)	General population	Miscarriage (siblings)	44/413	27989/1718	0.006	0.10	• Female CCS at increased risk of miscarriage
				Siblings	Live birth (all CCS vs general population)	1022/666	19335/2635	0.2	0.68	• No other differences noted
					Stillbirth (all CCS vs general population)	5/1683	94/16606	0.52	0.52	
Haggar et al. 2014	1894	4138	0	General population	**UNABLE TO DO META-ANALYSIS DUE TO LACK OF RAW DATA**					• Female CCS at increased risk of miscarriage, GDM, pre-eclampsia, haemorrhage, caesarean, hospitalisation post-partum
										• Female CCS have no excess risk of premature labour, antepartum haemorrhage, PROM,

						labour prolongation, retained placenta
Mueller et al. 2009	1898	14278	0	General population		• Offspring of female CCS at increased risk of premature birth and LBW • No increase of congenital abnormalities, growth restriction, neonatal complications or perinatal deaths in offspring of female CCS • Female CCS more likely to have preterm birth and LBW • Female CCS at no increased risk of congenital abnormalities, neonatal death

The outcomes reported by the authors included an extensive list of obstetric pregnancy and birth complications such as anaemia, gestational diabetes, pre-eclampsia, neonatal and fetal complications, live births, and pregnancy loss data. Detailed social demographics of the population were rarely reported, and control/comparison groups were not always matched rigorously within the CCS radiotherapy-exposed data sets. Sub-group analysis was not possible due to sample heterogeneity.

All 11 studies were classified as 'high' quality based on the NOS risk of bias assessment scale (defined in this review as a score of over 7 stars). Meta-analysis was possible for five outcomes. Three outcomes, Live birth (childhood cancer survivors who had radiotherapy versus survivors that did not), Live birth (childhood cancer survivors who had radiotherapy versus a non-childhood cancer affected control group) and low-birth weight (<2.5kgs) (childhood cancer survivors who had radiotherapy versus survivors who did not have radiotherapy), did not meet the criteria for heterogeneity (I^2 result of >50% or χ^2 result with a p value significance of <0.05).

Three of the meta-analysis outcomes, premature birth, stillbirth, and miscarriage met the criteria of significance. Increased odds of premature birth (<37 weeks gestation) (OR 3.69 CI [2.82, 4.81] p= < 0.00001) (Table 2) and miscarriage (OR 1.59 CI [1.37, 1.84] p=< 0.00001) (Table 3) were found when female CCS exposed to radiotherapy were compared to non-exposed CCS. Female CCS exposed to radiotherapy to the abdominal area were also found to have increased odds of stillbirth (OR 1.72 [1.08, 2.74] p= 0.02) (Table 4) when compared to non-CCS controls. This supports the findings of Signorello et al (2010) who reported that radiotherapy to the uterine area significantly increased the risk of stillbirth and neonatal death of female CCS when delivered at doses greater than 10 Gy (Gray).

Table 2 - Premature birth (CCS exposed versus non-exposed CCS)

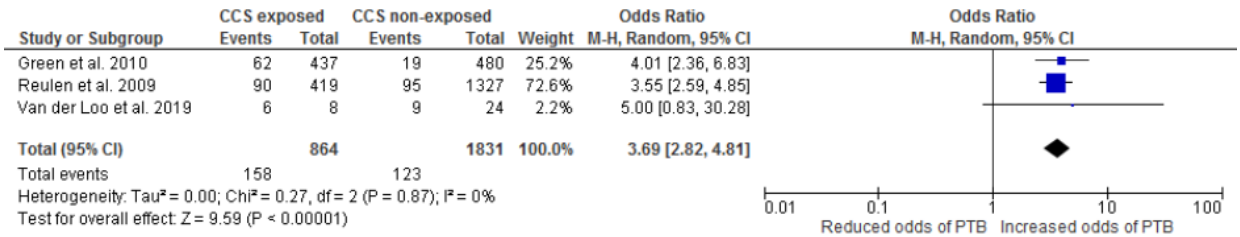
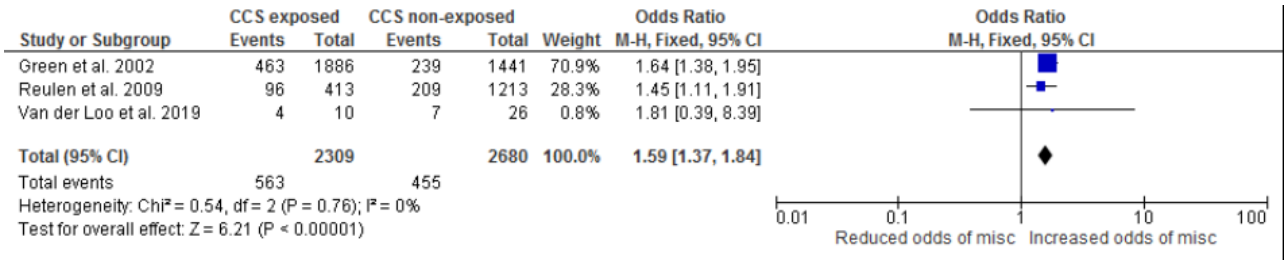


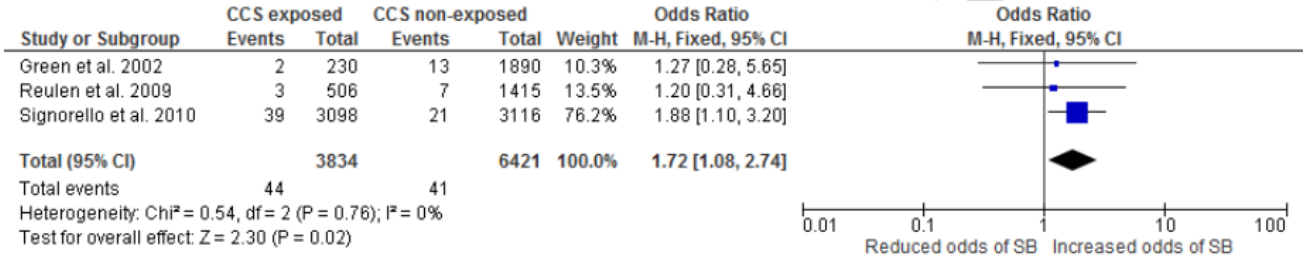
Table 3 – Miscarriage (CCS exposed versus non-exposed CCS)



Study or Subgroup	CCS exposed Events	Total	CCS non-exposed Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Green et al. 2002	463	1886	239	1441	70.9%	1.64 [1.38, 1.95]
Reulen et al. 2009	96	413	209	1213	28.3%	1.45 [1.11, 1.91]
Van der Loo et al. 2019	4	10	7	26	0.8%	1.81 [0.39, 8.39]
Total (95% CI)		**2309**		**2680**	**100.0%**	**1.59 [1.37, 1.84]**
Total events	563		455			

Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 6.21 (P < 0.00001)

Table 4 – Stillbirth (CCS exposed versus Non-CCS)



Study or Subgroup	CCS exposed Events	Total	CCS non-exposed Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Green et al. 2002	2	230	13	1890	10.3%	1.27 [0.28, 5.65]
Reulen et al. 2009	3	506	7	1415	13.5%	1.20 [0.31, 4.66]
Signorello et al. 2010	39	3098	21	3116	76.2%	1.88 [1.10, 3.20]
Total (95% CI)		**3834**		**6421**	**100.0%**	**1.72 [1.08, 2.74]**
Total events	44		41			

Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.30 (P = 0.02)

A narrative synthesis of the remaining data for additional adverse outcomes (see secondary outcomes) revealed congenital abnormalities were no more likely to occur in pregnancies of female CCS treated with radiotherapy to the flank, abdomen, or pelvis (Haggar et al 2014, Green et al 2010, Mueller et al 2009). Notably, female CCS with this treatment exposure history were found to have an increased risk of low-birth-weight babies (van de Loo et al 2019, Haggar et al 2014, Reulen et al 2009, Mueller et al 2009, Signorello et al 2006, Green et al 2002), however meta-analysis was not possible due to control group variance. This increased risk was not reflected in the limited data for small-for-gestational-age babies, supporting the theory that radiotherapy damage is linked to abnormal pathophysiology of the uterus. Extensive control group variation between the studies prevented meta-analysis for any additional outcomes as identified in the secondary outcomes of this review.

Notably, the narrative data within the included studies, were highly suggestive of an increased risk of maternal and fetal adverse outcomes such as hypertension (OR 3.6) or pre-eclampsia (OR 17.07) (Green et al 2010, Lie Fong et al 2010). Birth complications such as malposition of the fetus (OR 4.06), haemorrhage (OR 9.16) and manual removal of the placenta (OR 6.71) (Reulen et al 2017, Green et al 2010,

Lie Fong et al 2010). Meta-analysis was not possible as data were not reported within three studies or more, however further research is recommended to evaluate this potential risk. Future prospective longitudinal research with comparable control and CCS controls would be advised to provide more rigorous comparisons and evidence to support a correlation with these life-threatening perinatal complications.

Discussion

This review reported a link between female CCS treated with radiotherapy to the abdomen, flank or pelvis as a child/adolescent/young adult, and an increased odds of premature birth, stillbirth, and miscarriage. The results from this review support a growing body of evidence for health-care professionals responsible for the obstetric care of female CCS (van der Kooi et al 2021). Despite this evidence base, an increased awareness of future pregnancy and childbirth risk by health-care professionals is needed, alongside a multi-disciplinary communication model to facilitate optimal management CCS in pregnancy and birth.

Implications and recommendations for maternity care

A high-risk pregnancy care plan is recommended for female CCS, in particular if exposed to radiotherapy to the abdomen, flank or pelvis as a child. This recommendation should be communicated to the patient and their family as early as possible in pregnancy to allow for timely referral to a high-risk obstetric team. The recent publication by van der Kooi et al (2021) supports this recommendation and provides an excellent example guidance document for health care professionals. However, the guidance by van der Kooi et al (2021) gives no specific clinical interventions or surveillance methods. The guidance also has limited generalisability when applied to NHS maternity care systems and the UK midwifery care model for pregnancy. Wallace et al in 2013, produced guidance to assist with the risk-stratification of CCS in Scotland, highlighting pregnancy as a notable risk. However, a more specific and collaborative care pathway is needed to reflect patient need and encourage multi-disciplinary working and early referral for expert advice.

Obstetric and maternity care providers should consider the evidence and implement increased surveillance and/or interventional measures for radiotherapy-exposed female CCS in pregnancy. This may help to reduce the risk of adverse outcomes such as miscarriage, premature birth, and stillbirth. Examples of such interventions

include early pregnancy ultrasound scanning, serial cervical length assessment and early induction of labour. However, further evidence is needed to assess the need and impact of such interventions upon adverse outcomes.

Likewise, the increased odds of premature birth, miscarriage and stillbirth in this patient group highlights potential health economic ramifications. Prevention of miscarriage, pre-term birth and stillbirth have all been identified by the National Health Service (NHS) as key priorities for improvement, in the health care of pregnant women (NHS England, 2016a, NHS England, 2016b, National Institute of Health and Care Excellence (NICE) 2015). Health care costs arising from a premature birth costs the NHS millions per year and extends to costs associated with maternal psychological distress, birth trauma, infection, perineal trauma, and post-natal depression (NHS England, 2016a NHS England, 2016b, NICE, 2015, Tommys, 2018a, Tommys, 2018b). Therefore, the increased risk of premature labour in female CCS, warrants further consideration and economic analysis by maternity services. Furthermore, more qualitative studies in this area would be recommended to explore and evaluate the psychological experiences surrounding future pregnancy and birth of female CCS.

However, achieving a tailored pregnancy care package for CCS is a challenge for maternity services, who are already under pressure with an increasing number of women with highly complex medical histories and multiple co-morbidities requiring an individualised and multi-disciplinary care approach (NHS England, 2016a, NHS England, 2016b), CCS are an increasing population, with multi-variate individual and complex needs (Reulen et al 2009). CCS are also 60% more likely to have a co-morbidity related to their prior cancer treatment, which in turn is amplified if they have received radiotherapy (Aslett et al 2007). This puts female CCS into a high-risk population. Clinical guidelines for women in pregnancy with complex medical histories has led to a marked reduction in perinatal morbidity, stillbirth rates and maternal deaths (e.g., guidelines for epilepsy, congenital heart conditions) (NHS England 2020). This success in the reduction of adverse outcomes for complex health populations serves as an exemplar and demonstrates the need for an evidence-based guideline for this patient group.

Maternity care professionals must actively support and advocate birth choices of women in pregnancy, even in cases of complex medical and psychological need (NHS England, 2016a, NHS England, 2020). The needs of the woman and her family should be upheld to ensure that women are cared for, and give birth in the right place, at the right time, with the right professional leading their care; a model advocated by the Maternity Transformation Programme (NHS England, 2020). Despite this, no referral care pathway or clinical guideline exists for women with a history of CCS in pregnancy. A clinical guideline for maternity care in collaboration with NICE, The Royal College of Midwives (RCM) and The Royal College of Obstetricians and Gynaecologists (RCOG) is needed to support the standardisation of maternity care for this patient group, based upon existing evidence and the results of this review.

Additionally, the communication of risk for future adverse outcome in pregnancy and birth for female CCS exposed to radiotherapy to the abdomen, flank or pelvis is an important issue to be addressed by further research. Female CCS and their families should be informed and empowered to be active partners in their pregnancy care. They should also be provided with a full clinical picture of evidence-based research to make informed health care choices. The communication of potential risks should take place during or after cancer treatment, in the pre-conception period and/or very early in pregnancy. This recommendation is supported by van der Kooi et al (2021) and van de Loo et al (2019). Further research exploring how female CCS feel about future pregnancy and birth after treatment is also needed to provide health care professionals with context from which to design a patient-centred care pathway.

Research into toxic radiotherapy thresholds of the uterus is lacking, as demonstrated in the review (Reulen et al 2009). This evidence is needed to ensure that female CCS survivors treated with radiotherapy can be risk stratified. This would also ensure that any obstetric interventions or enhanced surveillance during pregnancy is directed to those only at very high-risk of complications.

Limitations and strengths

This review reported no significant result for the primary outcome ‘live birth’ (due to insufficient and heterogeneous data). ‘Live birth’ was found to be under-reported or unclassified as an outcomes within the data. This might be explained by a historical

tendency in quantitative research to measure or report solely adverse event outcomes within a patient group, however this assumption has not been explored (Smyth et al 2011). Risk of bias assessment utilised a recognised tool suitable for the assessment of cohort studies of population-based cohorts. However, there is a possibility that relevant studies were not included due to the extensive inclusion criteria or terminology of the key words used within the databases. The risk of publication bias is also present due to the inclusion of only peer-reviewed journal studies.

Evidence surrounding pregnancy and birth outcomes of female CCS is limited in quantity, quality, and bears little resemblance to modern treatments for childhood/young adult cancers. Included studies in the review acknowledged missing data in their results, pertaining to treatment modality and correct dosage information. Likewise, data included in this review relies heavily on self-reported patient outcomes. Self-reported outcome data collection facilitates recruitment of adequate sample sizes, however, is often criticised due to the potential for significant recall bias of participants (e.g., participants were typically asked to recall information about miscarriages and pregnancies via questionnaire) (Overbeek et al 2012). This could lead to data being reported that is not representative of the population and/or significant loss of data and un-generalisable results (Overbeek et al 2012). Ambiguous data surrounding radiotherapy toxicity thresholds for organs such as the uterus and the associated risk of adverse effects in future pregnancy and birth, suggests a need for more in-depth research, reflective of the advancements and up-to-date treatments for children with cancer.

Data registries used in this review represent the cohorts from the BCCSS (Hawkins et al 2008), CCSS (Robison et al 2002) and the Dutch DCOG LATER-VEVO study (Skion Later, 2020). In the CCSS a large cohort of 20,276 eligible five-year survivors of childhood and adolescent cancer were recruited (with a diagnosis prior to age 21 years between 1970–1986). The CCSS study addressed important long-term health issues related to treatment for CCS in the United States of America (Robison et al 2002). The UK registry, the BCCSS, aimed to determine the risks of adverse health and social outcomes among childhood cancer survivors diagnosed between 1940 and 1991, and who had survived five years. The BCCSS cohort of 17,981 forms the basis of many population-based studies of late mortality, including the risks/causes

of second malignant neoplasms by using national registration systems (Hawkins et al 2008). The Dutch registry counterpart is more recent, with 1944 CCS recruited with a data collection period of 2008-2014 (Skion Later, 2020).

The cancer registry data sets discussed above, although vast and detailed, do not adequately reflect recent novel treatments, dosages, or risk stratifications. Patient cohorts were relatively young when data were collected, limiting data from CCS of reproductive age and their reproductive outcomes. A more recent or prospective data collection method for CCS and subsequent reproductive outcomes would be beneficial.

Patient and Public Involvement and Engagement (PPIE) is rare within a systematic review. Traditionally, research studies perform an analysis of secondary data sources to answer a research question, with the aims of the study being completely researcher driven. However, clinical academic researchers are now encouraged to prioritise the needs and views of the patients within their research design, allowing for faster translational impact of their results into clinical practice (INVOLVE, 2017). This patient-driven, collaborative approach to research is also supported by the James Lind Alliance (James Lind Alliance, 2021). They as an organisation, lead priority setting partnerships for areas of need. They work together with multi-disciplinary and multi-stakeholder groups, to prioritise research questions of direct relevance to patients (James Lind Alliance, 2021). Using a collaborative PPIE approach within research methodologies, including systematic reviews, helps to improve the applicability, relevance and justification of important research questions and is recommended for future studies of this kind.

This review utilised a collaborative PPIE approach, to ensure that the selected outcomes of the review were of direct relevance to the patient group. However, it is acknowledged that PPIE inclusion could have been further embedded to include activities within the review team, the development of the research question and in the oversight of the meta-analysis process.

Conclusion

Female CCS who have received radiotherapy to the flank, abdomen or pelvis as a child have increased odds of premature birth (<37 weeks gestation) (OR 3.69 CI [2.82, 4.81] p= < 0.00001) and miscarriage (OR 1.59 CI [1.37, 1.84] p=< 0.00001)

when compared to CCS not exposed to radiotherapy. CCS exposed to radiotherapy to this area as a child also have increased odds of stillbirth (OR 1.72 [1.08, 2.74] p= 0.02) when compared to non-CCS controls.

Female CCS treated with radiotherapy to the flank, abdomen or pelvis warrant early high-risk antenatal care referral and ongoing surveillance throughout pregnancy. Female CCS and their families require detailed communication of future treatment-related pregnancy risk from health-care professionals when considering pregnancy in adulthood. Further investigation into the toxic radiotherapy thresholds of the uterus is needed to ensure that female CCS survivors can be risk-stratified for obstetric interventions in future pregnancy care. This in turn will assist to achieve optimal outcomes and shared decision making for female CCS in future pregnancy and birth.

Abbreviations

BCCSS	British Childhood Cancer Survivorship Study
CCS	Childhood cancer survivor (diagnosed between the ages of 0-24 years old inclusive)
CCSS	Childhood Cancer Survivorship Study
CI	Confidence Interval
EU	European Union
HEE	Health Education England
IVF	In Vitro Fertilisation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NOS	Newcastle Ottawa Scale
OR	Odds Ratio
PPIE	Public and Patient Involvement and Engagement
RCM	Royal College of Midwives
RCOG	Royal College of Obstetricians and Gynaecologists
UK	United Kingdom
USA	United States of America

Ethical Approval

This study was approved by Coventry University Ethics, project numbers P46688 and P60599.

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Contributors

AP conducted the review and PPIE survey, data collection and analysis, statistical analysis and writing of the review. EB provided support as director of studies and preparation and review of the manuscript. JC and BP reviewed the manuscript and provided supervisory support to the review, including the first draft of the publication. NA contributed as the second reviewer of data.

Declarations

We declare no competing interests or conflicts of interest. The author declares no permissions required or commercial affiliations. Supporting data related to this review can be obtained by emailing the author at polanco2@uni.coventry.ac.uk.

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