Review

Melanoma in pregnancy: Diagnosis and management in early-stage and advanced disease

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Abstract   Approximately one-third of women diagnosed with melanoma are of child-bearing age. The annual incidence of melanoma has risen steadily over the last 40 years, resulting in increasing numbers of women diagnosed with melanoma both during pregnancy, and post-partum. To date, there are no formal guidelines on the management of pregnancy associated melanoma (PAM), both early stage and metastatic. This article reviews the existing literature and provides a framework for the investigation and multidisciplinary management of PAM.
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1. Introduction

The annual incidence of melanoma has been rising steadily over the last 40 years, with current estimates at 3−5/100,000 in Mediterranean countries to over 50/100,000 in Australia and New Zealand [1]. Whilst incidence peaks around 65 years of age, melanoma can arise at any age and approximately one-third of female patients diagnosed with melanoma are of child-bearing age [2], with one study suggesting that 1% of female melanoma patients were pregnant at diagnosis [3]. This, combined with the global trends towards delayed childbearing, means that increasing numbers of women are diagnosed with melanoma during pregnancy. Pregnancy associated melanoma (PAM) is usually defined as any melanoma diagnosed during pregnancy or up to one-year post-partum [4], and requires careful investigation and management in a multidisciplinary approach involving both oncological and obstetric input. There remains significant debate around the effects of pregnancy on the pathophysiology of melanoma, with conflicting data on whether PAM carries a

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poorer prognosis than equivalent disease in non-pregnant or post-partum women [5]. Furthermore, there are no formal guidelines on the management of PAM. This article reviews the pathophysiology and aetiology of PAM and proposes guidelines for the diagnosis, investigation, monitoring and multidisci-plinary management of patients diagnosed with PAM.

2. Pathophysiological effects of pregnancy on melanoma

Whilst there is no convincing evidence that pregnancy is an independent risk factor for developing melanoma, there are a number of pathophysiological factors which have been studied for their impact on melanoma development during pregnancy [2], discussed below, and summarised in Fig. 1. To date, no single factor has been
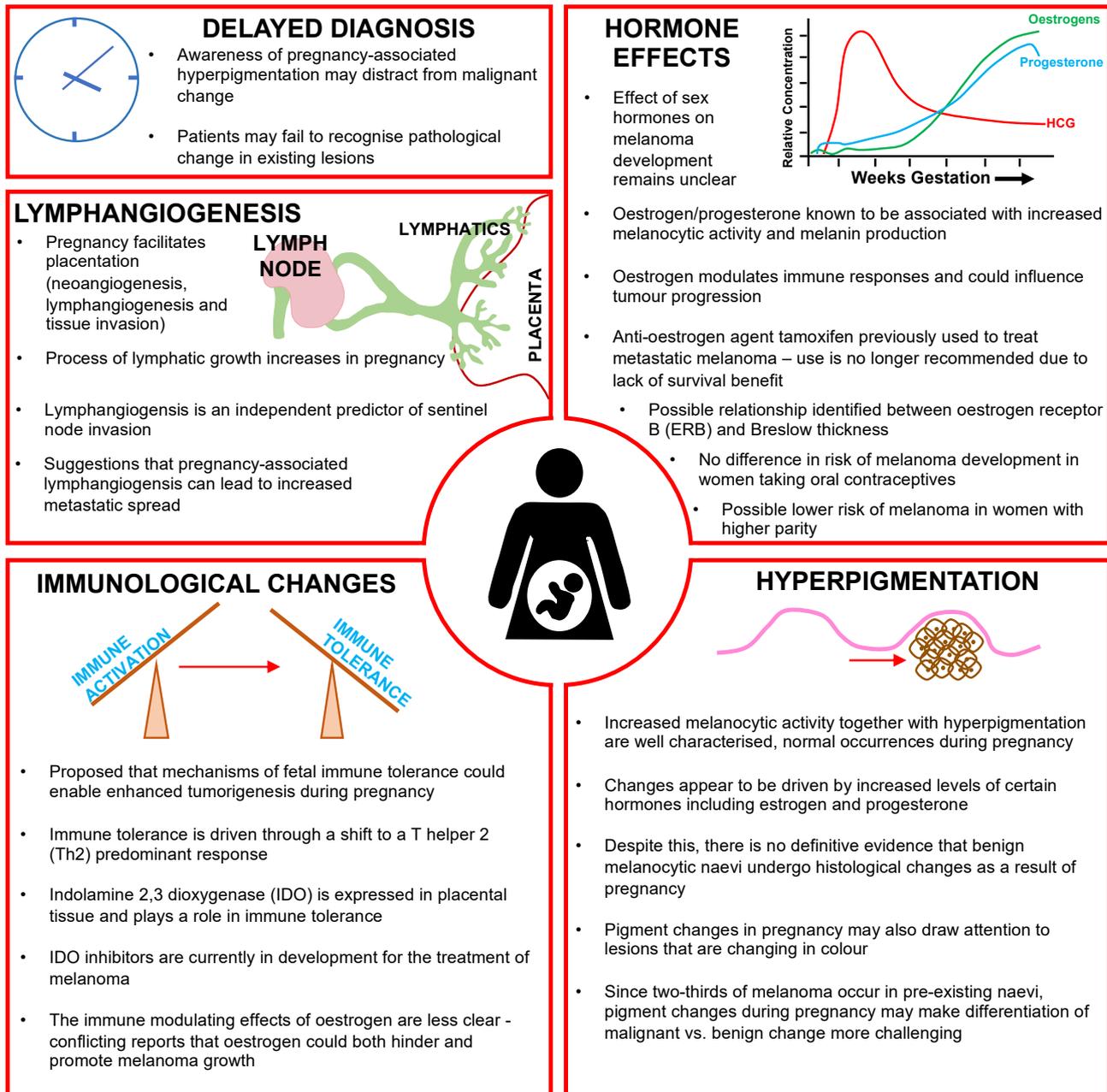

DELAYED DIAGNOSIS
- Awareness of pregnancy-associated hyperpigmentation may distract from malignant change
- Patients may fail to recognise pathological change in existing lesions

LYMPHANGIOGENESIS
- Pregnancy facilitates placentation (neoangiogenesis, lymphangiogenesis and tissue invasion)
- Process of lymphatic growth increases in pregnancy
- Lymphangiogensis is an independent predictor of sentinel node invasion
- Suggestions that pregnancy-associated lymphangiogensis can lead to increased metastatic spread

HORMONE EFFECTS
- Effect of sex hormones on melanoma development remains unclear
- Oestrogen/progesterone known to be associated with increased melanocytic activity and melanin production
- Oestrogen modulates immune responses and could influence tumour progression
- Anti-oestrogen agent tamoxifen previously used to treat metastatic melanoma – use is no longer recommended due to lack of survival benefit
  - Possible relationship identified between oestrogen receptor B (ERB) and Breslow thickness
    - No difference in risk of melanoma development in women taking oral contraceptives
    - Possible lower risk of melanoma in women with higher parity

IMMUNOLOGICAL CHANGES
- Proposed that mechanisms of fetal immune tolerance could enable enhanced tumorigenesis during pregnancy
- Immune tolerance is driven through a shift to a T helper 2 (Th2) predominant response
- Indolamine 2,3 dioxygenase (IDO) is expressed in placental tissue and plays a role in immune tolerance
- IDO inhibitors are currently in development for the treatment of melanoma
- The immune modulating effects of oestrogen are less clear - conflicting reports that oestrogen could both hinder and promote melanoma growth

HYPERPIGMENTATION
- Increased melanocytic activity together with hyperpigmentation are well characterised, normal occurrences during pregnancy
- Changes appear to be driven by increased levels of certain hormones including estrogen and progesterone
- Despite this, there is no definitive evidence that benign melanocytic naevi undergo histological changes as a result of pregnancy
- Pigment changes in pregnancy may also draw attention to lesions that are changing in colour
- Since two-thirds of melanoma occur in pre-existing naevi, pigment changes during pregnancy may make differentiation of malignant vs. benign change more challenging

Fig. 1. *Possible effects of pregnancy on melanoma.* A number of factors have been suggested as impacting upon the development of melanoma or disease kinetics in pregnancy, none of which have been shown to be clinically relevant. These include the impact of hormonal changes, the impact of hyperpigmentation on identification of suspicious lesions and delay in diagnosis, foetal immune tolerance which results in systemic immunomodulation, and pregnancy associated lymphangiogenesis which could drive early sentinel lymph node met-astatic spread [2,6–9,11,12,17,18,21–27].

proven to be an independent risk for melanoma development or progression during pregnancy, and a pooled-analysis of 10-case control studies of over 5000 women found no definitive association between pregnancy and risk of either developing melanoma, or a more aggressive disease trajectory [6].

2.1. Hyperpigmentation and delayed diagnosis

Pigment changes are normal during pregnancy, driven in part by hormonal changes [7]. Hyperpigmentation could both draw unnecessary attention to benign lesions or distract from malignant lesions, leading to delayed recognition of melanoma for patients and clinicians [6,8,9]. For these reasons, any pigmented lesion which changes its clinical or dermoscopic characteristics during pregnancy should be treated as suspicious.

2.2. Lymphangiogenesis immunological change

The unstable genetics within cancer cells can lead to the recapitulation of embryogenic developmental processes [10] and one physiological pathway shared between placentation and tumourigenesis is (lymph)angiogenesis. Pregnancy is therefore a proangiogenic state (predominantly in the womb) although there is little evidence that pregnancy associated systemic angiogenesis is clinically significant. There is some evidence that measuring the extent of local melanoma lymphangiogenesis could be a sensitive predictive marker for the presence of lymph node metastases [11], and some pre-clinical *in-vivo* data that this process may accelerated in pregnancy [12].

Furthermore, tumours and embryos both need to evade the 'host' immune system in order to survive. During pregnancy, inactivation of the maternal immune response occurs at the placental interface, mediated by unique trophoblast cells [13]. Malignant tumour cells are able to hijack many trophoblastic features in order to manipulate their local microenvironment to evade host immune responses. Downregulation of MHC class I expression, increased surface expression of PDL-1, and activation of indoleamine 2,3-dioxygenase (IDO), are all immunosuppressive actions shared between trophoblasts and tumour cells [10,14,15]. Whilst blockade of the PD-1/PDL-1 axis is an established treatment in increasing numbers of solid tumours, to date, inhibition of IDO has so far failed to demonstrate clinical efficacy in the treatment of melanoma, with further trials ongoing [16].

2.3. Hormone effects

Increased levels of oestrogen and progesterone are known to be associated with increased melanocytic activity [17] but there is no definitive evidence that hormonal changes can drive melanoma development or progression [18]. Until the introduction of immune checkpoint inhibitors and BRAF-directed therapy, the selective oestrogen receptor modulating agent tamoxifen was utilised as a treatment in stage IV melanoma including as part of regimens such as the Dartmouth treatment regimen (dacarbazine, cisplatin, carmustine, and tamoxifen) [19]. Whilst a number of studies demonstrated improved response rates in poly-chemotherapy regimes that also contained tamoxifen, no improvement in overall survival was seen in comparison to single agent chemotherapy [19,20] and its use is no longer recommended in the treatment of melanoma.

3. Effects of melanoma on pregnancy

There is no evidence that a diagnosis of primary melanoma during pregnancy results in any increased risk of adverse outcomes for the foetus [9], with only anecdotal evidence that a diagnosis of PAM may result in increased rates of infants that are large for their gestational age, with ongoing research working to explore this association [2]. There is also no evidence that patients with BRAF-mutant PAM have different outcomes than their BRAF-wildtype counterparts [28]. In some patients diagnosed with advanced PAM, early delivery or even termination of pregnancy may be recommended (see below; Investigation and Management of Pregnancy Associated Melanoma) and management of these patients should be conducted together with the experienced obstetric teams [29].

3.1. Placental and transplacental metastatic spread

Whilst metastatic spread to the placenta is rare, melanoma accounts for around 30% of the reported cases of this [2,30]. Placental involvement is indicative of widespread haematogenous dissemination in the mother, with no reported cases of placental involvement in the absence of other sites of visceral metastatic disease. Quantifying the risk of placental involvement is difficult given the low patient numbers, with one retrospective French series identifying only one case of placental spread in a series of 22 patients diagnosed with stage III/IV melanoma during pregnancy [31]. Furthermore, placental involvement does not necessarily mean that the foetus will be affected, a phenomenon that is rarer still. In 2002, a comprehensive review identified 27 cases of placental metastasis over the preceding 40 years [32], with 6 (22%) of these cases also reporting foetal metastatic spread [32]. Based on this study and a few case reports [33,34] it is widely accepted that foetal involvement can be reasonably excluded in the absence of macro- or microscopic placental involvement [35]. Outcomes are generally poor for affected foetuses, with the majority of infants (>80%) dying from disease [32]. Despite this, there are occasional reports of spontaneous post-partum regression in the infant [30,34]. Overall, estimates are that around 25% of infants born in the presence of placental metastases will die from metastatic melanoma [30]. In all cases reported, maternal outcomes

were consistent with era-dependent survival rates for stage IV melanoma.

Women diagnosed with stage IV disease during pregnancy should be counselled on the rare possibility of placental and foetal spread, and thorough macroscopic and microscopic placental histological evaluation should be performed for all patients. In the presence of placental involvement, careful neonatal clinical examination and follow up should be conducted.

4. Prognosis of pregnancy associated melanoma

Current understanding is that melanoma in pregnant women does not carry a significantly poorer prognosis than for non-pregnant women, and it is the stage of disease which remains the most important factor to take into account during counselling patients diagnosed with PAM.

There is conflicting evidence whether a diagnosis of localised melanoma during pregnancy carries a poorer long-term prognosis when analysed in terms of differences in Breslow thickness [36], overall recurrence rates and mortality. A number of publications over the last few decades draw conflicting conclusions, with some reporting that pregnancy has no effect on prognosis [5,37], whilst others report poorer prognosis in PAM [38,39] (Table 1). A nationwide cohort study from Norway (160 patients diagnosed during pregnancy with 4460 controls) reported a slightly increased mortality rate in PAM (HR 1.52, CI 1.01—2.31, P = 0.047) [39]., A Swedish study with similar patient numbers (185 patients diagnosed during pregnancy with 5348 controls) reported no difference [40]. In view of this disparity, a number of recent meta-analyses have been performed, covering studies dating back over the last 40 years, with some suggesting no difference in mortality for women diagnosed during pregnancy [37,41], and others suggesting that mortality in this group is significantly higher [38,42]. Reasons for this disparity may be down to methodology, and the fact that many of the studies investigated have small cohort sizes or are not sufficiently corrected for confounding variables [5].

5. Investigation and management of pregnancy-associated melanoma

Following standard rapid cancer referral for a suspicious lesion during pregnancy, all women, regardless of gestation, can safely undergo an excisional biopsy under local anaesthetic, or an incisional biopsy in the case of large lesions, or those located on the palms, soles or face [50]. Indeed, even if patients require general anaesthetic, a systematic review of over 12,000 women undertaking non-obstetric surgical intervention found no increased risk of miscarriage or birth defects [51]. Following confirmation of melanoma, appropriate investigations depend upon (i) the gestational age/trimester and (ii) the tumour stage as per the American Joint Committee on Cancer (AJCC) staging system (Table 2). Timing of the wide local excision (WLE) needs to be considered in the context of decisions regarding sentinel LN biopsy as outlined below.

5.1. Stage 0—II disease

For pregnant women diagnosed with stage 0 melanoma, no further staging procedures are needed. For those diagnosed with stage IA melanoma, staging is completed by clinical examination alone [50]. For all other patients diagnosed with stage IB—IIC melanoma, evaluation for regional lymph node (LN) and in-transit metastases is required to determine whether patients are truly stage I/II or whether they have stage III disease.

In non-pregnant patients, regional LN ultrasound scan (USS) with fine needle aspiration (FNA) of any radiologically suspicious LNs should ideally be performed prior to WLE at the primary site. Furthermore, at the time of the WLE, sentinel LN biopsy (in the absence of radiologically suspicious LNs) using ^{99m}technetium labelled radiocolloid is recommended for those patients with primary melanoma of Breslow thickness > 0.8 mm [52]. The decision whether to proceed with these additional staging investigations during pregnancy can be difficult, and must take into account the gestational age, the risks of LN involvement based on the primary melanoma staging, and whether or not the patient will

Table 1

Studies examining the prognosis of pregnancy-associated melanoma since 2001.

Year	Article type	Location	# of PAM* patients	Control patients	Conclusion	Ref.
2003	Case-Control	Netherlands	46	368	No Difference	[43]
2004	Cohort	Sweden	185	5348	No Difference	[40]
2005	Cohort	USA	412	2451	No Difference	[44]
2006	Case-Control	Italy	10	30	No Difference	[45]
2009	Cohort	Norway	160	4460	Poorer Prognosis	[39]
2010	Case-Control	Israel	65	11	Poorer Prognosis	[46]
2013	Cohort	UK	306	16,222	Poorer Prognosis	[47]
2014	Case-Control	USA	18	18	No Difference	[48]
2014	Cohort	Sweden	1019	5838	No Difference	[49]

In some studies, the definition of PAM varies, with some studies limiting PAM to melanoma diagnosed only during pregnancy, and some including post-partum diagnoses, either six months or one year following delivery.

Table 2
Cutaneous melanoma staging.

AJCC Stage	Description
Stage 0	In situ melanoma (T_{is})
Stage I A	Breslow thickness < 0.8 mm without ulceration (T1a)
Stage I B	0.8–1 mm thick without (T1a) or with ulceration (T1b)
	< 0.8 thick with ulceration (T1b)
	1–2 mm thick without ulceration (T2a)
Stage II A[a]	1–2 mm thick with ulceration (T2b)
	2–4 mm thick without ulceration (T3a)
Stage II B[a]	2–4 mm thick with ulceration (T3b)
	> 4 mm thick without ulceration (T4a)
Stage II C[a]	> 4 mm thick with ulceration (T4b)
Stage III A	< 1 mm with/without ulceration *and* 1–3 occult metastases in regional LNs
	1–2 mm without ulceration *and* 1–3 occult metastases in regional LNs
Stage III B	No evidence of primary tumour *and* 1 clinically detected metastasis in regional lymph nodes *or* presence of *in-transit*, satellite, and/or microsatellite metastases
	< 1 mm with/without ulceration *or* 1–2 mm without ulceration *and* 1–3 metastases in regional LNs (at least one clinically detected), or *in-transit*, satellite, and/or microsatellite metastases
	1–2 mm with ulceration *or* 2–4 mm without ulceration *and* 1–3 occult *or* clinically detected metastases in regional LNs or *in-transit*, satellite, and/or microsatellite metastases
Stage III C	No evidence of primary tumour *and* > 2 LN metastases (at least one clinically detected), *or in-transit*, satellite, and/or microsatellite metastases with at least 1 tumour-involved LN *or* any number of matted nodes with/without *in-transit*, satellite, and/or microsatellite metastases
	<2 mm with/without ulceration *or* 2–4 mm without ulceration *and* > 4 LN metastases *or in-transit*, satellite, *and/or* microsatellite metastases with at least 1 tumour-involved LN *or* any number of matted nodes with/without *in-transit*, satellite, and/or microsatellite metastases
	2–4 mm with ulceration *or* >4 mm without ulceration and any metastases in regional LNs *and/or* presence of *in-transit*, satellite, and/or microsatellite metastases
	> 4 mm with ulceration and 1–3 occult or clinically detected regional LN metastases *or* in transit, satellite, and/or microsatellite metastases with 0–1 tumour-involved LN
Stage III D	>4 mm with ulceration *and* > 4 tumour-involved LNs *or in-transit*, satellite, *and/or* microsatellite metastases with two or more tumour-involved LNs *or* any number of matted nodes with/without *in-transit*, satellite, *and/or* microsatellite metastases
Stage IV	Any primary size, any regional lymph node status *and* distant metastases

Eighth edition of the AJCC clinical (and pathological) staging for cutaneous melanoma [56]. AJCC: American Joint Committee on Cancer. LN: Lymph node.
[a] To define a patient a true stage II, SLNB must be performed. Without SLNB, patients are clinical stage II, but not pathological stage II.

proceed with adjuvant treatment and whole body imaging should the biopsy be positive [53]. Whilst the radiation dose to the foetus from the radio-colloid is not harmful at any gestational age [54], there is a small risk of anaphylaxis from blue dyes, as well as a potential teratogenic risk within the first trimester [4]. One small-scale study of maternal and foetal outcomes in 15 patients following SLNB demonstrated no adverse outcomes or events, including in the three patients who had LN clearance surgery for micro-metastatic disease [55].

Although SLNB can therefore be performed safely during pregnancy, the question is whether it is necessary. If the SLNB is positive, adjuvant treatment cannot be offered with a foetus in situ. In many cases, it is therefore reasonable to wait until the baby has been delivered before performing the SLNB. Furthermore, if initial resection margins are clear, WLE could also be delayed allowing a more accurate SLNB to be performed post-partum. If a high-risk melanoma is found in the first trimester and the woman wishes to have a termination in the event of a positive SLNB, so that she can receive adjuvant treatment without delay, it is reasonable to promptly perform WLE and SLNB.

A proposed SLNB management algorithm is shown in Fig. 2. For patients with pT1b-pT4a disease (with clear resection margins), it is reasonable to consider offering regular USS imaging of the draining lymph node basin during pregnancy and delaying WLE and SLNB until post-partum. For any patient with positive resection margins, WLE should be performed promptly. Patients with pT4b disease are at higher risk of having microscopic and macroscopic metastatic disease. In these patients, it is reasonable to perform staging investigations with whole body MRI scan, and if no macroscopic disease is seen, to discuss WLE and SLNB. As above, the only reason to perform SLNB during pregnancy and not wait until post-partum is if the mother is willing to consider a termination in the event of a positive SLNB to facilitate timely adjuvant therapy.

Presently, patients diagnosed with stage II disease are not eligible to receive adjuvant therapy, despite the prognosis for stage IIB and IIC disease being poorer than for patients diagnosed with IIIA and IIIB disease, respectively (Table 3). It is probable that in the future this recommendation will change; these patients should
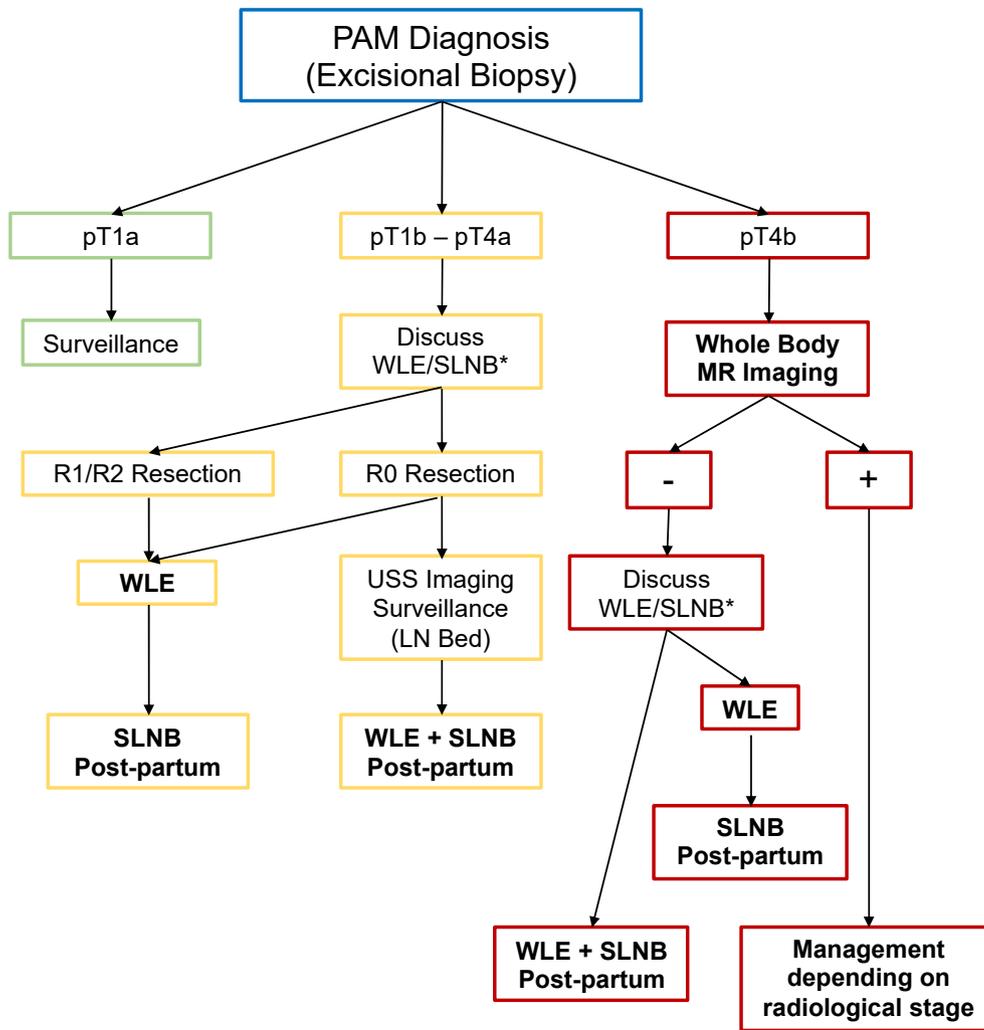
Fig. 2. **Management algorithm for sentinel-lymph node biopsy in PAM.** Proposed pathways for timing of SLNB based on tumour stage and gestational age [4,57]. R0: Clear resection margins, R1: microscopic tumour at resection margin, R2: macroscopic tumour at resection margin. *Discussion should include the reasons for WLE and SLNB, the risks of these procedures to mother and foetus and the risks of delaying investigations in high risk disease.

then be counselled as if they have stage III disease and may benefit from adjuvant therapy. Under these circumstances in many cases it would still be reasonable to delay adjuvant treatment until the post-partum period.

5.2. Stage III disease

A positive SLNB, resected macroscopic LN disease and/or in-transit metastases identifies patients with stage III disease who are eligible for one year of systemic adjuvant therapy with either BRAF-directed treatment [58] or immunotherapy [59,60] depending on their BRAF mutational status, in view of their recurrence risk (Table 3, better visualised using the Kaplan Meier curves based on the eighth edition of the AJCC staging [61]). Either of these adjuvant treatments

Table 3
Melanoma-specific according to stage. Bold values are the average for each stage.

AJCC Clinical/ Pathological Stage	Five-year survival (%)	Ten-year survival (%)
I	**98%**	**95%**
II	**90%**	**84%**
III	**77%**	**69%**
IA	99%	98%
IB	97%	94%
IIA	94%	88%
IIB	87%	82%
IIC	82%	75%
IIIA	93%	88%
IIIB	83%	77%
IIIC	69%	60%
IIID	32%	24%

From the eighth edition International Melanoma Database [56].

can reduce recurrence risk by up to 50%. Adjuvant melanoma treatment is not recommended during pregnancy due to the possibility of foetal abnormality/loss, but a careful conversation is required with PAM patients that takes into account gestational age, the index of suspicion of stage III disease and the risks of recurrence for those PAM patients with confirmed stage III disease. This discussion should cover the risk of relapse (7% at 5 years for stage IIIA *vs.* 68% at 5 years for stage IIID disease [56]), the potential risk reduction with treatment, and the potential short and long-term side-effects of therapy. This will allow the patient to make a decision as to whether to proceed with SLNB, and to understand the consequences of a positive SLNB.

For those patients in their first trimester at high risk of disease relapse, the conversation must also cover the option of termination of pregnancy in order to proceed with early adjuvant therapy. Finally, all patients must be counselled on breast feeding, which is not recommended whilst on adjuvant treatment.

For women presenting with palpable nodal disease in pregnancy (presumed stage III), whole body staging should be performed using imaging modalities that protect the foetus (see below; Imaging surveillance during pregnancy). Assuming no distant disease is detected, a therapeutic lymphadenectomy should be performed regardless of gestational age. Post-operative discussion regarding adjuvant treatment should follow as above. Finally, patients may rarely present with unresectable stage III disease. In such cases, investigation and management should be as per stage IV melanoma.

5.3. Stage IV disease

It is usually impossible to adequately manage the mother's stage IV disease whilst she is pregnant. Under these difficult circumstances, termination or early induction should be considered where possible. This would facilitate appropriate staging investigations and treatment with systemic agents that can be life-saving.

These conversations should be carried out with the support of the obstetrics team. For the patient to make an informed decision, she needs to understand:

1. What the immediate threat is to her from the metastatic disease — this will depend on the distribution and volume of disease and disease kinetics (i.e. LDH levels, symptoms, and the pace of spread);
2. The rare but recognised risk of trans-placental spread;
3. Her prognosis post-pregnancy — she may not wish to proceed with the pregnancy if she has a low chance of survival from her metastatic disease. Discussion of family circumstances should she not survive should be encouraged;
4. Risks and benefits of systemic anti-cancer treatments.

5.3.1. Systemic treatment

For patients with stage IV melanoma there are few conclusive data to support the use of either immunotherapy or BRAF-directed treatments during pregnancy, and limited evidence of the potential harmful effects of these medications on pregnancy and lactation. Isolated case reports of their use do exist in patients who wished to continue their pregnancy, or who became pregnant whilst on treatment. Knowledge of these isolated reports should provide a useful adjunct to facilitate patient counselling should systemic treatment be immediately warranted in patients who wish to continue their pregnancy against medical advice.

5.3.1.1. BRAF-directed treatment. To date, three BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) have been approved for use in BRAF-mutant melanoma [62], and they are now usually used in combination with MEK inhibitors (cobimetinib, trametinib, binimetinib) to enable more complete blockade of the MAPK pathway [63], except in patients who have a contraindication to MEK inhibition (i.e. cardiac dysfunction). It is generally accepted that the combinations of dabrafenib with trametinib or encorafenib with binimetinib have a more favourable toxicity profile than that of vemurafenib with cobimetinib.

In pre-clinical studies, vemurafenib has demonstrated low-level transmission from mother to foetus, whilst dabrafenib was shown to be teratogenic and embryotoxic at doses three times the standard human exposure [64]. Although encorafenib has not been tested in pre-clinical studies, it is thought to possess potential to cause foetal harm [65]. MEK inhibitors are classified as potentially teratogenic; they should be avoided where possible during pregnancy [66]. If used, patients need to be made aware of the potential for harm. A limited number of case reports have been published on the use of BRAF-directed therapy in pregnant patients and these are summarised in Table 4. All case reports were of vemurafenib, the first BRAF targeted drug to be licenced for BRAF mutant stage IV melanoma, with no studies found on the use of combination BRAF and MEK inhibition. Of these 4 studies, all four infants were born prematurely (24—36 weeks), with one report of foetal growth restriction. No infants had long term complications. Maternal outcomes and survival were in line with that expected of stage IV melanoma treated with BRAF-directed therapy.

5.3.1.2. Immunotherapy. Three immunotherapy (IO) drugs are currently licensed for use in patients with metastatic melanoma; the anti-CTLA4 monoclonal antibody (mAb) ipilimumab and the two anti-PD1 mAbs, nivolumab and pembrolizumab. Treatment

Table 4
Case-reports of BRAF-directed treatment in pregnant patients.

Year	Drug	Weeks gestation[a]	Maternal age	Outcome	Ref.
2013	Vemurafenib	25	37	Marked foetal growth restriction − emergency c-section at 30 weeks. No congenital malformations.	[67]
2018	Vemurafenib	22	30	Severe skin toxicity after 12 days, spontaneous pre-term delivery of twins at 24 weeks gestation, maternal death from intracranial haemorrhage 78 days after treatment initiation	[68]
2017	Vemurafenib	20	25	Induction of labour at 34 weeks with admission of the neonate to NICU to control a supraventricular tachycardia. Mother switched to double IO following delivery.	[69]
2019	Vemurafenib	17	29	Partial response in the mother with no foetal toxicity. Normal delivery at 36 weeks gestational age with no evidence of placental or foetal involvement.	[70]

[a] At initiation of treatment. IO = Immunotherapy.

options include doublet IO therapy (ipilimumab with nivolumab), and singlet IO therapy (pembrolizumab or nivolumab), with individual treatment decisions based on a number of factors including performance status (PS) and patient choice [71]. Similar to BRAF directed therapy, IO is not recommended for use in pregnancy, especially given uncertainty over the role that immune checkpoint molecules including PD-1 and CTLA-4 have on immune homeostasis during pregnancy [72]. To the best of our knowledge there are currently only seven case reports describing the use of IO in pregnant patients with stage IV melanoma (six cutaneous melanoma, one uveal melanoma). Two cases describe the use single agent nivolumab, one using single agent

Table 5
Case-reports of immunotherapy treatment in pregnant patients.

Year	Drug(s)	Weeks gestation[a]	Maternal age	Outcome	Ref.
2013	Ipilimumab	7[b]	32	Neonate delivered healthy via normal delivery at term with no developmental abnormalities. Mother had clinical evidence of PD prior to delivery.	[73]
2016	Nivolumab	6[b]	31	Spontaneous premature labour at 33 weeks gestation. Foetus showed signs of moderate intrauterine growth restrictions and was born with IO induced congenital hypothyroidism. CR in the mother.	[74]
2016	Ipilimumab + Nivolumab	9	34	Significant hepatic toxicity after 4 cycles of doublet IO and 1 cycle of singlet IO. Subsequent PD with new cerebral metastases. Placental insufficiency detected at 32 weeks with subsequent c-section performed. Neonate born healthy with no evidence of melanoma and no developmental delay.	[75]
2017	Ipilimumab + Nivolumab	18	34	PD on treatment after two cycles. Emergency c-section at 24 weeks gestation, with maternal death after this. Placenta positive for melanoma metastases, but neonate showed no signs of illness and remained disease free and developmentally normal.	[76]
2020	Ipilimumab + Nivolumab	11[b]	32	Twin pregnancy complicated only by iron deficiency anaemia, requiring IV iron infusion, and foetal growth restriction. Delivery by caesarean section at 32 weeks gestation. Pathology review of placenta demonstrated no melanoma presence.	[77]
2021	Nivolumab	6[b]	39	Nivolumab suspended following discovery of twin pregnancy. Patient developed HELLP syndrome so delivery was performed at 30 weeks gestation. One twin was missing a hand − thought to be from amniotic cord strangulation. Placenta unremarkable. Normal development of both children.	[78]
2021	Pembrolizumab	21	40	Diagnosed with metastatic disease at 10 weeks gestation. Pembrolizumab administered from 21 weeks' gestation and infant was delivered healthy at 28 weeks. Placenta normal. Mother switched to ipilimumab/nivolumab post-partum. No developmental issues in the infant.	[79]

[a] At initiation of treatment, IO = Immunotherapy.
[b] Conceived on treatment, CR = Complete Response, PD = Progression of Disease. HELLP: haemolysis, elevated liver enzymes, low platelet count.

ipilimumab, three using ipilimumab and nivolumab in combination, and one using pembrolizumab monotherapy, summarised in Table 5.

In four cases, patients conceived whilst on IO treatment, and in the other three, treatment was initiated urgently during pregnancy. Six of the seven pregnancies ended prematurely (24−33 weeks) with one baby born at term. Four infants from three pregnancies (one set of twins) (42%) showed evidence of intrauterine growth retardation and one case had placental metastases at birth. One twin pregnancy was complicated by HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count), a rare, pre-eclampsia associated complication, which requires prompt delivery. All infants survived with no long-term complications, and maternal outcomes were consistent with that expected in stage IV melanoma treated with IO therapy.

5.3.1.3. Chemotherapy. Due to poor response rates, chemotherapy is no longer widely used in melanoma and use remains limited to selected patients who have exhausted immunotherapy and targeted treatment options and who remain fit enough for systemic treatment [4,80]. Prior to recent advances, the main chemotherapy agents used were dacarbazine, which is reportedly teratogenic in animals, and temozolomide, for which limited case-reports exist on inadvertent use in pregnancy. From 5 case reports, 4 reported no adverse foetal outcomes, with 1 reporting neural-tube defects and cerebral palsy, which are recognised effects of sodium valproate which this patient was also taking. Regardless of this, given the lack of survival benefit with chemotherapy in stage IV melanoma, there is no role for chemotherapy in PAM.

5.3.1.4. Radiotherapy. Provided the uterus is outside the treatment field and protected from scattered radiation, radiotherapy is feasible during pregnancy [81] but in the context of stage IV melanoma will only be effective for isolated sites of oligometastatic disease, for example, isolated brain metastases [4]. Newer modalities such as stereotactic radiotherapy, intensity-modulated radiation therapy (IMRT) and proton beam therapy should be utilised where possible if pregnant patients require radiotherapy since they will minimise foetal exposure without compromising on therapeutic dose [82].

6. Imaging for staging and surveillance during pregnancy

Clinical imaging is a vital tool in both the staging and surveillance of patients with a diagnosis of melanoma. In normal circumstances imaging surveillance with computed tomography (CT) or PET-CT ± brain imaging (CT *vs.* MRI) is offered to all patients with high-risk stage IIB-C, stage III and stage IV disease,

often on a 3−6 month basis for 3−5 years, with exact recommendations dependant on recurrence risk and local practice [83]. There are no specific guidelines regarding imaging for staging or surveillance in PAM, where staging is important due to the implications regarding the health of the mother and foetus.

Ionising radiation (CT, PET-CT, X-ray (XR)) is a recognised cause of miscarriage, foetal growth restriction, mental impairment and microcephaly. Ionising radiation has a threshold dose above which these effects may occur, and the potential severity of these effects is dose-dependent above this threshold [84]. In addition to this, there are potential carcinogenic and mutagenic risks to the foetus, with ongoing debate as to whether this leads to any significant subsequent risk of childhood malignancy [85,86]. In reality, there is no 'safe' level of ionising radiation exposure in pregnancy that is universally accepted, and the general consensus is that attempts should be made to minimise exposure whilst obtaining sufficient clinical information [87]. Studies suggest that there is no increased risk of miscarriage or major malformation/growth restriction at doses of 50 mGy, when compared with the natural background radiation during pregnancy (0.5−1.6 mGy) [88]. Further studies suggest a 0.1% risk of complications at exposures of > 250 mGy [89], with a typical CT scan of the chest, abdomen and pelvis exposing the foetus to between 10 and 50 mGy per scan [90]. Any potential risks to the foetus should be balanced against the clinical benefit of the imaging study [87], and the stage of pregnancy at which exposure occurs is a key determinate in the level of risk of harm to the foetus. Given these potential risks, it is important to consider the optimal imaging modality in pregnancy, aiming to achieve the highest diagnostic sensitivity with the lowest possible radiation exposure, including avoiding the use of ionising radiation where feasible, with ultrasound (US) imaging and magnetic resonance (MR) imaging the most widely utilised in pregnant women. Whilst MRI imaging is deemed safe from the second trimester onwards, gadolinium-based contrast agents should be avoided [91]. Concerns have been raised that scanning at higher Tesla Fields (i.e. 3T, rather than the more commonplace 1.5T) may lead to increased risk of hearing difficulties in the foetus, but so far this has not been proven [92,93]. Some advantages and disadvantages of available imaging modalities are summarised in Box 1, along with the indications for their use in PAM.

In lactating or breastfeeding patients, there remains a question of whether contrast agents are safe for use or not, and evidence regarding this is limited [94], with some centres advocating precaution with all contrast agents, and others suggesting that only a very small number of gadolinium based agents carry a risk [95]. In view of this, standard advice is to

Box 1. Imaging Modalities in PAM: Advantages, Disadvantages and Indications [84,90,97−105].

XR Imaging:
Advantages: Low radiation exposure, particularly if foetus is not within the radiation field.
Disadvantages: Not adequately sensitive to monitor disease.
Indications: No indication in PAM. but XR generally acceptable in pregnancy in clinically indicated.
US Imaging:
Advantages: Safe in pregnancy with no foetal adverse outcomes reported, high sensitivity (96%) to detect draining LN bed metastases.
Disadvantages: Should be limited to 30 minutes due to theoretical risk of temperature increase and to keep acoustic levels as low as possible. US machines should be configured for obstetric use. Not sensitive enough for whole body imaging with sensitivity of 53%.
Indications: Indicated in PAM to evaluate draining LN bed (especially in first trimester).
CT Imaging:
Advantages: Quick to perform and high sensitivity to detect distant metastases (85%).
Disadvantages: High risk in terms of radiation exposure to foetus, with radiation exposure dependent upon number and spacing of imaging sections and whether foetus is within the field. Contrast media also carries a risk of adverse events including anaphylaxis.
Indications: CT imaging should be avoided in PAM. unless there is no viable alternative, and adequate counselling has taken place.
PET Imaging:
Advantages: Can detect metabolically active distant disease with higher sensitivity than plain CT (94%).
Disadvantages: Discouraged due to the radiation risk to the foetus, although exact risk and dose remains uncertain.
Indications: Not recommended in PAM. unless it is felt that clinical need outweighs risks and adequate counselling is performed along with attempts to minimize foetal radiation exposure.
MR Imaging:
Advantages: Whole-body (WB) MRI is a sensitive and effective imaging modality for detecting both bone and soft tissue and bone pathology. WB-MRI is a valid alternative to PET-CT, including in melanoma.
Disadvantages: Not recommended in first trimester due to risk of acoustic and thermal injury. Gadolinium contrast agents to facilitate CNS imaging should be avoided as this is teratogenic in animals.
Indications: Whole-body imaging modality of choice in PAM in second and third trimester, but should be avoided in the first trimester unless benefits outweigh potential risks.

interrupt breastfeeding for between 12- and 24-h following administration of iodinated or gadolinium-based contrast agents, following counselling of the mother [96].

7. Uveal melanoma in pregnancy

Despite a common origin from neural crest-derived cells, uveal and cutaneous melanoma have limited overlapping genetic signatures and are considered to be distinct conditions [106]. BRAF mutations are almost never seen [107], and uveal melanoma (UM) is generally resistant to standard immunotherapy approaches. Uveal melanoma is aggressive in behaviour, with up to 50% patients experiencing distant metastatic relapse, most often in the liver [106], with a sustained long-term risk requiring lifetime surveillance.

Similar to cutaneous melanoma, there is evidence for sex hormone receptor expression in UM, particularly for oestrogen receptor (ER), oestrogen-related receptor alpha (ERRα), luteinising hormone (LH) receptor, and luteinising hormone-releasing hormone (LHRH) receptor [108,109]. Whilst there are anecdotal reports of aggressive disease during pregnancy, case−control studies report no difference between 5-year survival rates between pregnant and non-pregnant patients [110], nor do exogenous hormones (oral contraceptives or hormone replacement) have an impact on the risks of developing UM [111]. What is less clear is whether ER is a potential treatment target in UM, with studies ongoing to establish this [108].

For patients with a history of UM, surveillance with 6 monthly liver US/MR scans can continue as normal during pregnancy, and for patients diagnosed with UM during pregnancy, local treatment for UM should be offered as standard with pregnancy posing no contraindication to these treatments [109]. In the rare event that patients are diagnosed with stage IV UM during pregnancy, or become pregnant with stage IV UM, counselling should occur in line with that of stage IV cutaneous melanoma, with careful emphasis placed on the poorer prognosis associated with relapsed UM.

8. Counselling for future pregnancies

For many women, fertility will become an increasing issue with time, and advice to avoid pregnancy during what may be her limited remaining fertile years may not be in her or her potential family's interests. Equally however, it is important to highlight that a relapse of disease could significantly shorten her life. The only way to give accurate and practical advice to a woman is to; i) discuss what the risk of relapse is according to the features of the primary melanoma; ii) discuss the surveillance program that is recommended; iii) discuss the risk of death from her disease and iv) discuss whether she and her partner (if present) would want more children were she not to survive to see them grow up. Once all these factors have been taken into account, the patient will be in a position to decide whether she wishes to proceed with and plan for subsequent pregnancies.

Following a diagnosis of stage I/II disease, some have suggested advising against future pregnancy for 2−3 years. However, this does not take into account the timeframe for recurrence of thin and intermediate thickness melanomas (see Table 3) and is therefore not recommended. In many of these patients who do relapse, this often occurs more than 2−3 years following initial diagnosis. Considering a no-pregnancy period after diagnosis of a T4b lesion is more justifiable given the higher risk of early recurrence in these patients. However, for many women, this may be during their period of greatest fertility and therefore an individualised conversation taking into account the issues above should take place. There is no evidence that subsequent pregnancies impact upon overall risk of relapse [42], nor do pregnancy associated hormonal factors impact upon risk of relapse or pace of disease [37], with some anecdotal evidence suggesting it may be protective [40]. The main concern in female patients of child-bearing age with a prior diagnosis of melanoma would be the impact of relapse during or immediately after pregnancy, and patients should be made aware of the implications of this prior, taking into account their overall risk of relapse, as well as the possible implications of interruptions to standard surveillance during her pregnancy.

More complex scenarios arise in the cases of (i) patients treated with immunotherapy for stage IV disease who achieve sustained complete responses after two years of treatment, or (ii) patients with high risk stage III disease who have completed adjuvant treatment. These patients may wish to consider having children and the challenge faced by treating clinicians is how best to advise patients regarding the timing of future pregnancies in the face of evolving datasets on long term outcomes. From current data, survival/relapse rates appear to plateau 3−4 years following treatment initiation in stage IV/III patients [112,113]. In view of this, it is reasonable to advise patients to have at least 2 years of intensive surveillance following the end of treatment for stage IV disease, or at least one year for those completing adjuvant treatment. Patients must be adequately counselled on the ongoing recurrence risk, as well as the potential need for an interruption to their surveillance. Recommendations should be individualised taking into account the patients age, perceived risk of future relapse and personal choice.

8.1. Fertility preservation

Prior to initiating adjuvant treatment for stage III melanoma, many centres are increasingly recommending fertility preservation prior to starting treatment. Whilst none of the treatments licenced for use in the adjuvant setting (dabrafenib, trametinib, pembrolizumab, and nivolumab) are gonadotoxic, long term effects of these treatments on fertility are poorly understood [114] and

in the case of immunotherapy agents, there is a risk of potentially significant autoimmune side effects including endocrinopathies, which can requiring life-long treatments and have the potential to affect fertility [115]. Whilst there is no doubt that further research is needed to enable clinicians to effectively counsel patients on the long-term effects of these treatments on their fertility, it is vital that discussions around fertility are central to conversations with women of child-bearing age embarking adjuvant treatment for melanoma [116], with referrals to fertility services where appropriate.

9. Conclusions and recommendations

Management of both early stage and advanced PAM should be a multidisciplinary approach involving oncologists, dermatologists and obstetric teams. Careful patient education should be conducted to ensure that women understand the implications of the diagnosis and the potential risks to both themselves and their unborn child. Whilst there is a scarcity of scientific literature on the subject, this is an advancing field, and international prospective studies of outcomes in PAM are planned. The recommendations made within (and summarised below) this article should serve to guide clinicians in tailoring individualised treatment and counselling advice to PAM patients, based not only of the features of their disease but also on their gestational age at diagnosis.

9.1. Recommendations

- There is no definitive evidence that melanoma diagnosed during pregnancy is associated with poorer outcomes, or that pregnancy impacts upon disease progression or pace.
- Excision of primary melanoma is safe and should not be delayed in pregnancy, and should be performed under local anaesthetic where possible.
- Decision to perform sentinel lymph node biopsy should take into account trimester of pregnancy, features of the primary melanoma and the wishes of the patient. Delaying SLNB (plus WLE) until the post-partum period is reasonable in many cases, particularly as adjuvant therapy cannot commence until after delivery.
- Regular US surveillance of the draining LN bed is reasonable during pregnancy. If delayed WLE and SLNB are planned, 12-week US surveillance is acceptable.
- Women of child-bearing age undertaking adjuvant treatment for stage III melanoma should receive counselling on future fertility, including referral for fertility preservation if appropriate.
- In patients presenting with macroscopic stage III disease, lymphadenectomy after staging should be performed. Deferral of post-surgery adjuvant treatment until the post-partum period or termination and earlier initiation of adjuvant treatment should be discussed.

- For patients with stage IV disease, termination of pregnancy or early induction should be discussed to facilitate optimal management of the mother.
- Systemic treatment (immunotherapy and targeted therapy) should only be used during pregnancy in life threatening stage IV disease following careful counselling of the mother.
- There is no role for chemotherapy even in life-threatening situations due to poor response rates.
- CT imaging should be avoided in pregnancy, unless clinical need outweighs risk.
- Ultrasound is the imaging modality of choice in the first trimester.
- Whole-body MRI is the imaging modality of choice from the second trimester onwards.
- Contrast media (including gadolinium) should be avoided in all stages of pregnancy.
- Counselling on future pregnancies should be offered for all women of child-bearing age, and should be based upon their individual *risk of disease relapse.*

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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