Master of Science in Dermoscopy and Preventive Dermato-Oncology

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Dermatoscopic features of naevi during pregnancy - a systematic review

Written by

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Declaration of Authorship:

I hereby declare that the thesis submitted is my own work. All direct or indirect sources are acknowledged as references. The Master Thesis was not used in the same or similar version to achieve an academic degree.

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Dr Ioana Cosgarea Newcastle upon Tyne, 25/07/2021

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I would also like to thank my parents for their continuous support in my academic development.

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1. Zusammenfassung

Veränderungen in melanoytäre Naevi und Neubildung von Naevi sind Ereignisse die während der Schwangerschaft berichtet wurden und der Zusammenhang zwischen Schwangerschaft und Melanom ist ein umstrittenes Thema. Das Ziel dieser Arbeit was ein „systematische Review“ durchzuführen um dermatoskopische Veränderungen in Naevi die während der Schwangerschaft auftreten zu identifizieren, die zur Unterscheidung zwischen Naevus und Melanom hilfreich sein können. Hierzu wurden die Datensätze Medline, Scopus und Embase nach Studien überprüft, wo Melanome und Naevi in schwangere Patienten dermatoskopisch unersucht charakterisiert wurden.

Sechs Studien mit insgesamt 258 Patienten und 1167 untersuchte Hautlesionen wurden im hiesigen Review eingeschlossen. In keiner der Patienten wurde ein Melanom diagnostiziert. Neubildung von Naevi wurde in weniger als die Hälfte der Patient beobachtet. Die häufigste beobachtete dermatoskopische Veränderung war die erhöhte Anzahl von „dots“ – Punkte. Neubildung von Blutgefässen, hypo- und hyperpigmentierte Areale und Veränderungen in Pigmentnetzwerk waren häufig beobachtete dermatoskopische Charakteristika.

Die Patienten wurden in drei der eingeschlossenen Studie postpartum nachverfolgt und die dermatoskopischen Veränderungen die während der Schwangerschaft aufgetreten sind waren reversibel in der 6 beziehungsweise 12-monatigen Nachuntersuchung.

Die eingeschlossenen Studien waren sehr heterogen so das ein direkter Vergleich der Studien nicht möglich war. Gut durchgeführte Studie sind dringend notwendig um Naevi in der schwangeren Population kritisch zu beurteilen und zu analysieren um hochrisiko dermatoskopische Strukturen für diese Patientengruppe zu identifizieren.

2. Abstract

Changes in melanocytic naevi and development of new naevi have been reported in pregnant women and the association between pregnancy and melanoma is a controversial topic. The aim of the present study was to conduct a systematic review to identify the dermatoscopic changes that occur in naevi during pregnancy that could facilitate in distinguishing benign from suspicious lesions. Medline, Scopus and Embase datasets were reviewed for clinical studies on dermatoscopic characteristics of melanoma and nevus in pregnancy. Six cohort studies with a total of 258 patients with 1167 skin lesions that were examined were included in the systematic review. None of the patients developed melanoma. Development of new naevi, when reported, was observed in less than half of the participants. The most frequent observed dermatoscopic change among the studies was the increase in the number of dots. Development of new vessels, hypo- and hyper pigmentations and changes in the pigment network were common described changes. Three of the included studies performed follow-up examinations postpartum and the dermatoscopic changes seen during the pregnancy, reversed at 6 and 12 months post delivery. The included studies were heterogeneous not allowing head-to-head comparisons between them. Robust studies of dermatoscopic evaluation of naevi in pregnant women are needed to determine high-risk. dermatoscopic characteristics.

3. Introduction

Melanocytic naevi undergo changes throughout the lifetime, with the total naevus count increasing in early adulthood up to midlife and thereafter decreasing due to involution (1, 2). There are several factors that can induce and influence changes in naevi, these factors being gender, age, UV-exposure, skin type and in female patients pregnancy. Changes in melanocytic naevi and development of new naevi have been reported in pregnant women (3, 4). Dermatoscopic changes during pregnancy have being described in some case repots or small cohort studies. These changes consist of size increase, darkening of the naevi, pronounced vascular pattern, development of globules or changes in network (5, 6).

It is mentioned that up to 1/3 of pregnant females notice naevi changes during pregnancy, however, studies looking into these found that the “naevi changes” are more frequent changes in non-melanocytic lesions such as fibroma pendulans or dermatofibroma (7)(13). Furthermore, a study that examined melanocytic naevi on pregnant female histologically found no significant changes between the study group and a control group, although a tendency of higher atypical in the pregnant participants was observed (8).

A study conducted on pregnant female with dysplastic naevus syndrome found that this group had a higher incidence of clinical naevus changes and dysplastic histological features in comparison to non-pregnant female (26).

The association between pregnancy and changes in naevi as well as the development of melanoma has been a controversial topic for a long time. Published literature reports on poor prognosis in female patients who develop a melanoma during pregnancy (5). It was found that there is a statistical difference between the Breslow thickness of melanomas in pregnant in comparison to non-pregnant females, suggesting that this might be due to a diagnosis delay in the latter group (23).

Data about pregnancy-associated melanoma (PAM), defined as melanoma that develops during pregnancy and up to one year postpartum, are

controversial as some suggest a worse prognosis compared to melanoma in nonpregnant patients, the former being reported with a 17% higher mortality rate (3, 9). Furthermore, in a recent Swedish population-based study, melanoma was the most common malignancy during pregnancy, followed by breast and cervical cancer (10). The worse outcome of PAM might be associated with the hormonal changes as well as the immune surveillance changes, however changes of melanocytic naevi during pregnancy may also play a role for delayed melanoma diagnosis.

The identification of dermatoscopic criteria of pregnancy-related naevi changes and melanoma features would aid in the early diagnosis of a PAM. Several case reports and reviews have been published reporting on PAM. However, the literature regarding dermatoscopic changes of naevi and melanoma during pregnancy is limited and consists of case reports and small cohort studies. In most studies describing dermatoscopic changes in naevi total body photography was rarely mentioned and the authors usually focused only on the dermatoscopic changes in a few of the patients lesions.

Therefore, the aim of this systematic review was to provide an overview of the literature and to help identify dermatoscopic criteria of naevi and melanoma during pregnancy that could aid in the early diagnosis of PAM.

4. Materials and Methods

4.1 Search Strategy

A review of the Medline, Scopus and Embase datasets for clinical studies published from 1989 to July 11, 2020, on dermatoscopic characteristics of melanoma and naevus in pregnancy was conducted.

For methodology and reporting we followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis), see Appendix Table 1. A protocol for the present systematic review was not prepared.

The words “melanoma”, “nevus”, “pregnancy” and “ dermatoscopy” were used to identify studies examining female patients which underwent skin examination using a dermatoscop during their pregnancy. Combinations of MeSH (Medical Subject Heading) terms and boolean operators applied in our search on Medline are listed in the following: melanoma OR melanoma, amelanotic OR nevus OR skin neoplasms AND pregnancy AND dermoscopy. Scopus was searched using the following combinations of MeSH terms and boolean operators: ("dermoscopy" OR "dermatoscopy") AND ("pregnancy" OR "pregnant") AND ("naevus" OR "nevus" OR "nevi" OR "nevi" OR "melanoma")). Combinations of MeSH terms and boolean operators used in our search on Embase included the following: ((nevus) OR (naevus) OR (metastatic melanoma) OR (mucosal melanoma) OR (melanoma) OR (non melanoma skin cancer) OR (amelanotic melanoma) OR (cutaneous melanoma) AND (dermoscopy) OR (epiluminescence microscopy) AND pregnancy).

Reference list of included articles were manually searched for further studies.

4.2 Study selection

Only articles published in the English or German language were considered for further review and duplicates were excluded. In order to address the anticipated overall lack of well-designed studies in large populations of pregnant patients who underwent dermatoscopic examination, we included prospective studies of any design and retrospective cohort analyses. Case reports, systematic reviews and meta-analyses were excluded from our

analysis. Articles were screened based on title and abstract to determine eligibility. Entire articles were reviewed and retrieved to assess acceptability.

4.3 Data Extraction and Quality Assessment

Data were extracted using a predesigned form. The quality of the included studies was rated using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies, Appendix Table 2, and risk of bias was assessed using the Chochrane Risk of Bias Tool, Appendix Table 3.

5. Results

The initial search identified a total of 73 studies and during the review process a further three articles were identified by manual searching of the reference lists. After duplicate articles were eliminated, a total of 42 articles remained. Papers were narrowed by title, abstract and full–text review. A total of six articles were included in the analysis.

The included studies consist of six cohort studies with a total of 258 patients summing up to 1167 skin lesions that were examined. A flowchart of article selection is provided in Figure 1 and an overview of the included studies in Table 1 and 2.

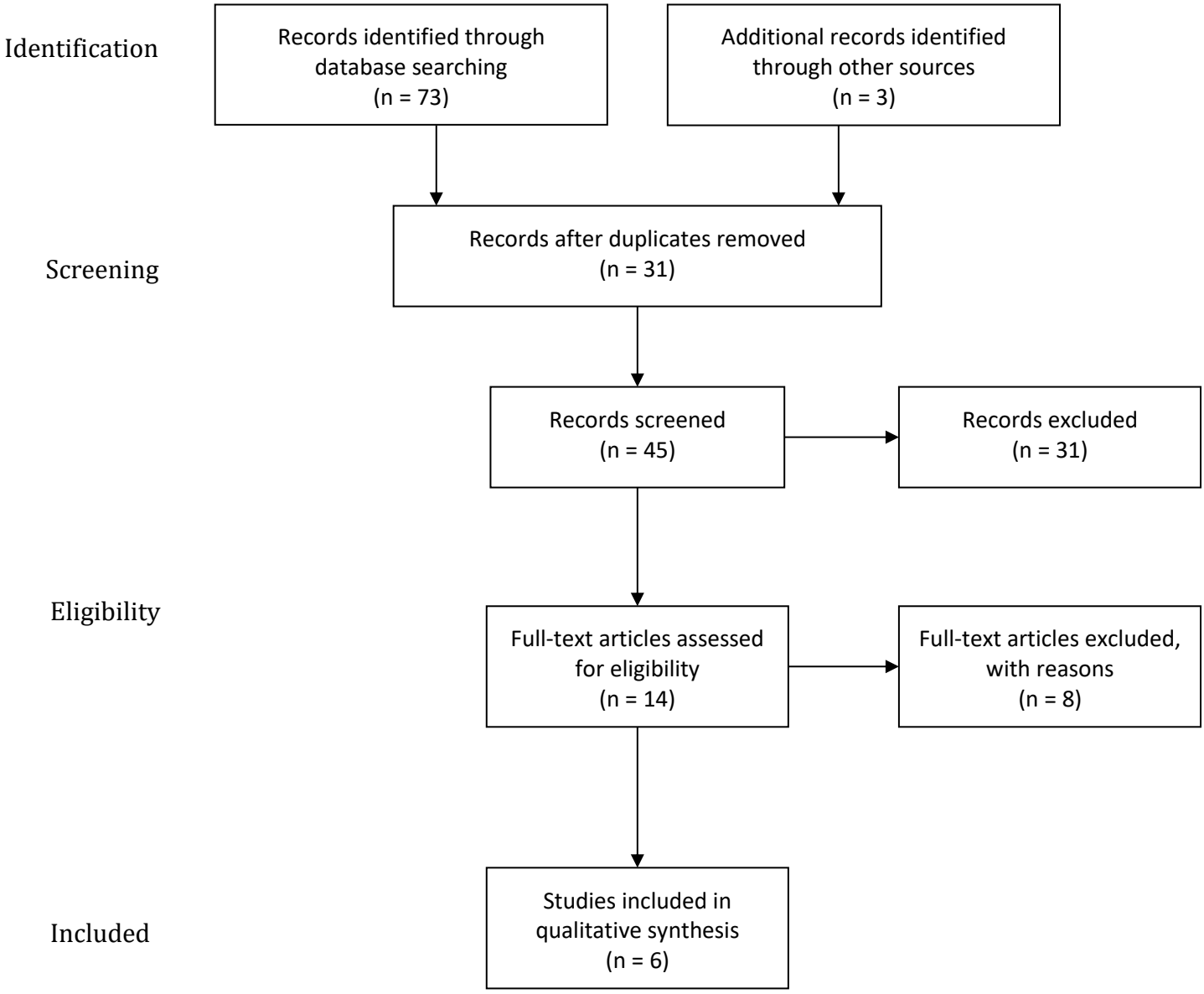

Figure 1. Flow Diagram of Study Selection.

Table 1. Characteristics of the included studies

Study	Design	Population	No. of participants	No. of analysed patients	Age, median, y	History of melanoma	Family history of melanoma	Follow-up duration
Aktürk et al, 2006 (Turkey)(11)	Observational monocentric study	women in the first trimester of pregnancy	77	56	26 ± 5.01	no	1 case	no follow-up
Rubegni et al, 2006 (Italy)(12)	Observational study	women in the first trimester of pregnancy and non-pregnant women	70 (35 pregnant women and 35 control)	70	34	NR	NR	12 months postpartum
Zampino et al., 2006 (Italy)(13)	Observational monocentric study	women in the first trimester of pregnancy	60	49	32.3± 3.5	NR	3 cases	6 months postpartum
Martins-Costa G.M, Bakos R, 2019 (Brazil)(14)	Observational monocentric study	Pregnant women with a minimum of 10 naevi	18	18	33± 3.49	1	4 cases	no follow-up
Gunduz et al, 2003 (Turkey)(15)	Observational monocentric study	women in the first trimester of pregnancy	21	21	26.8 ± 5.1	NR	NR	6 months post partum in 3 cases
Strumia, 2002 (Italy)(16)	Observational monocentric study	primigravidas with naevi larger than 4mm	12	12	36.2	no	no	no follow-up

Abbreviation: NR - not reported, no - number

Table 2. Clinical and dermoscopic characteristics

Study	No. of anaysed lesions (n)	Anatomical site (n)	Changes in lesion size, mean (mm)	Changes in colour	Dermatoscopic assessment	Changes in the total dermoscopy score	Pattern analysis	Dermatoscopic structures that changed during pregnancy	Developed melanoma (n)	Developed new naevi (n)
Aktürk et al, 2006 (11)	97	front of body 27, face and neck 21, upper extremities 18, lower extremities 10, gluteus and genital region 6	4.25 in first trimester vs. 4.59 in third trimester*	NR	total dermoscopy score - TDS (ABCD rule) and pattern analysis	2.17 in first trimester vs. 2.22 in third trimester*	yes	Increased dots no. (49 in first trimester vs. 55 in third trimester*)	no	3/56
Rubegni et al, 2006 (12)	204	NR	NR	darker globules, darker pigment network (increase in "CONTRAST" during pregnancy, decolouration postpartum)	DB-Mips® System		no	changes in the colour of globules and network	no	NR

Zampino et al., 2006 (13)	86	Back	Non-significant change in the measures of the area between all 3 examinations	lightening of the colour towards the end of pregnancy and postpartum	TDS (ABCD rule)	TDS increase by 2.37% at V2 and decrease by 5.27% at V3*	yes	less prominent pigment network, no. of vessels increased*	no	NR
Martins-Costa G.M, Bakos R, 2019 (14)	703	Abdomen 101, back 178, anterior chest 146, lower limbs 114, neck 39, face 28, upper limbs 93	55% of naevi enlarged	10.4% of cases increased pigmentation, 5,8% cases became hypopigmentation	pattern analysis, FotoFinder Moleanalyzer system, total body photography*		yes	network changes 23.2%, new dots and globules 12.4%, new vascular structures 3.2%, new streaks 1.7%, new structureless areas 1%	no	8/18
Gunduz et al, 2003 (15)	21	Back 10, face 6, neck 5	2 naevi increased in size	colour changed in 2 lesions	TDS (ABCD rule)	TDS higher in the third trimester vs first in 4 patients, returned to base line at 6 months follow-up	no	thickening of pigment network in 2 cases, development of radial streaming in 1 case, increase no., colour and size of dots and	no	NR

							globules in 2 cases			
Strumia, 2002 (16)	56	Abdomen 14, breast 5, forearm 18, back 6, hip and breast -9, unknown 4	increased size in the lesions on the breast and abdomen	no change	pattern analysis	yes	lesions with pigment network became wide-meshed and clearer, lesions with globular patter developed brown globules at the periphery	no	not included in the study	

Abbreviation: NR - not reported, no – number. * statistical significant

5.1 Study design

All six included studies were observational cohort studies, the majority (five) being monocenter. None of the studies commented on the sampling technique and only one study (12) had a control group.

The largest study was the one by Aktur et al. which included 77 participants (7) and the smallest study comprised 12 participants (16).

5.2 Clinical characteristics

The population analysed in the studies was made up of pregnant women, most in the first trimester of pregnancy, and non-pregnant women which were part of the control group in one study. One study included only primigravidas (16), a further one included only participants with a minimum of 10 naevi (14) and, as previously mentioned, only one study had an aged-matched control group (12, 17).

The median age among the studies ranged between 26 and 36.2 years, in four studies the median age being above 30 years.

Personal history of melanoma was documented in three studies and out of the whole participants only one participant had a positive history. Family history of melanoma was looked at in four studies and eight out of the 258 participants had a first-degree relative with a melanoma. The presence of dysplastic nevus syndrome was reported in one patient, while the presence of dysplastic nevus syndrome, congenital giant nevus and personal history of melanoma were deemed as exclusion criteria in another study (18).

Three studies also conducted a follow-up examination postpartum with the longest follow-up examination being at 12 months after delivery (12) (17).

The Fitzpatrick skin type was not documented in all studies, however, three studies were conducted in Italy, two in Turkey and one in Brazil, which included patients with skin type II, III and IV.

Between the six studies a total of 258 participants were included, but only 226 participants with melanocytic lesion were examined by dermatoscopy.

The description of the anatomical site of the lesions varied between the

studies, with one study lacking to report the anatomical site of the lesions. The majority of the lesions were located on the front of the body, including abdomen and chest, followed by the back, the extremities, face, neck and other regions such as genital, gluteal, hip; the detailed location of reported lesions is shown in Table 2.

In most studies the participants were examined twice, in the first and third trimester, while one study checked the participants in the second and third trimester. Three studies had a third examination, two at 6 months and one at 12 months postpartum.

5.3 Changes in naevi during pregnancy

An increase in size of the naevi was observed in most of the studies, however, only in one study the increase was statistically significant, from a mean increase of 4.25mm in the first trimester to 4.59mm in the third trimester (18) (Table 2). In the study by Martins-Costa et al. 55% of the naevi enlarged while in the study by Strumia et al. the enlargement of naevi only on the breast and abdomen was observed while lesion on the forearms and back remaining unchanged (14, 16).

One study observed that 8 (44%) out of 18 participants developed new naevi during the pregnancy (14). Another study recorded the development of new naevi but these were not included in the their analysis. The other studies did not comment on the development of new melanocytic lesion.

None of the 226 participants who had their naevi examined developed melanoma. In the study by Martins-Costa et al., the authors excised one lesion during the follow-up period as this was a new fast growing lesion, which the study participant developed in the third trimester, the histopathologic examination reporting it as a dysplastic melanocytic naevus (14).

5.4 Dermatoscopic changes

Dermatoscopic assessment of lesions was done by total dermatoscopy score (TDS) using the ABCD rule in three studies (13, 18, 19), one of them using also pattern analysis, the remaining studies used either pattern analysis alone (Strumia), pattern analysis, Fotofinder and Moleanalyzer system (Martins-

Costa) and the DB-Mips® System (12) (17). Pattern analysis was used as an assessment tool in four out of the six studies. Changes in the dermatoscopic score used were noted in the three studies using the TDS, all three studies reporting a higher TDS for the lesions examined in the third trimester versus the first. Two of the 3 studies reported that the TDS decreased or returned to base line at the follow-up examination postpartum which was in both studies after 6 months.

Changes in colour were reported in four studies. Rubegni et al noted darker globlues by dermatoscopy and increase in “contrast” during pregnancy, with decolouration of the same naevi 12 months postpartum (12) . Zampino et al. reported of lightening of the colour towards the end of pregnancy and at the 6 months follow-up examination (13). Martins-Costa et al. observed increased pigmentation in 10.4% of the lesions and hypopigmentation in 5.8% during pregnancy (14).

With regard to specific patterns, one study reported structural irregularity with more network irregularity and globules distribution as well as thickening of the pigment network, two studies did not find any change and three studies did not report on it.

Changes in the number of dots (increased number of dots) was the most frequent described dermatoscopic characteristic which changed during pregnancy. Akturk et al found a statistic significant difference between the number of dots in the first trimester in comparison to the third, dots were found in 49 naevi at the initial examination and in 55 naevi at the second examination in the third trimester (11). Martins-Costa et al. found an increase of 12.4% of new dots and globules during pregnancy, network changes in 23.2% of their patients, new vascular structures in 3.2%, new streaks in 1.7% and new structureless areas in 1 % (14). They also found that streak formation was more frequent within participants of skin type II rather than skin type III and IV, the difference being statistically significant. Increase in the number, colour and size of dots was also noted by Gunduz et al. in 2 cases (15). They also found radial streaming in one case and thickening of the pigment network in further two cases. In the study by Strumia, lesions with globular pattern developed brown globules at the periphery while lesions with pigment network became wide-meshed and clearer (16). Development of new

vessels was mentioned by two studies, the study by Zampino et al. mentioning an increased number of dotted and comma vessels during pregnancy (13).

6. Discussion

It has been reported that during pregnancy around 90% of women will undergo skin changes, including mole changes (20). The association between pregnancy and melanoma has been a hot topic for many years with reports supporting the idea that pregnancy increases the risk of melanoma (21). While single case reports of melanoma development during pregnancy (22) can be found in the literature, there are also several studies supporting the idea that pregnancy is not a risk factor for melanoma development (14, 23, 24).

In the present systematic review we included only cohort studies leaving out case reports. After reviewing six cohort studies, which included a total of 258 patients with 1168 naevi, the main finding of our analysis was that no patient developed melanoma. The development of new lesions during pregnancy was mentioned in three out of the six studies with only two studies documenting objectively the incidence of new naevi developing, total body photography was used only in one of the studies for documenting new naevi. Martins-Costa et al. reported that 44% of their participant developed new naevi while in Akturk et al study this was seen only in 5.3% (11, 14). With regard to the development of new naevi, it is currently unclear whether these naevi developed physiologically given a relatively young age of the women or are indeed caused by hormonal changes during pregnancy. Based on our review, the former hypothesis seems to be the more convincing one.

Increase in size of the examined naevi was noticed in all but one study. While some studies found the majority of the lesion increased in size (14) or even a statistical significant increase in size (11), another study found this only in lesion on anatomical sites who undergo distension during pregnancy such as abdomen or breast (16). In Gunduz study, which included lesion on the back, face and neck, increase in size was observed only in 2 naevi (15). It stands to reasons, that in naevi which increase in size during pregnancy and that are located in anatomic sites prone to distension, such as abdomen and breasts, the main cause for this change is mechanical rather than hormonal.

Changes in colour were addressed in four out of the six studies. An interesting finding was the observation that some lesions become more

hyperpigmentated during the pregnancy but the colour of the lesion lightens towards the end of the pregnancy or post partum. It has been shown that melanocytes as well as melanoma cells express functional estrogen and androgen receptors and that their activity is influenced by several factors including anatomic location (25). In pregnancy the number of estrogen and progesterone receptors on melanocytes increases and is responsible for the pigmentary changes that can be observed during pregnancy (26).

Three studies used the TDS for assessing the naevi dermatoscopically and in all three studies the TDS was higher in the third trimester compared to the first one. In the study by Aktruk et al. this difference was even found to be statistically significant (11). When following up the patients post partum, two studies, Zampino et al and Gunduz et al., mentioned a decrease of the TDS and return to the baseline TDS (15) (13).

The most frequent observed dermatoscopic change among the studies was the increase in the number of dots. In Akturk et al. study they notice that the number of lesion exhibiting dots between the first and the third pregnancy trimester increased from 49 to 55, while in the Martin-Costa study the increase was of 12.4% (11, 14). In Strumia's study it was noticed that naevi with a globular patter developed more peripheral brown globules and the studies by Rugbeni et al and Gunduz et al also mention changes and increased number of dots and globules (12, 15, 16). The presence of peripheral dots and globules seen with dermatoscopy is generally a sign of nevus growth (27) at young age, however, these pregnancy-related observations could be also result of the mechanical distension of the skin resulting in an upward movement of the basal layer with junctional or dermal nests becoming more easily visible by dermatoscopy (16).

Network changes have been observed in five out of the six studies. While some studies reported a less prominent network or a change into a broader wide-meshed network, others found that the network became more thickened and in some cases even developed radial streams, a sign generally associated with a malignant phenotype. Again, most of these changes may be attributable to the distension of some body parts, resulting in a thinned epidermis and subsequently, better visualization upon dermatoscopy.

Vessel formation during pregnancy was reported in two studies, in one being

observed in 12.4% of the cases (14), but appears to decrease again after delivery in the post-partum period. It is known that physiologic vascular changed happen during pregnancy and that these are as a response to the production of placental hormones such as estrogens and human chorionic Gonadotrophin (28, 29). The dermatoscopic vascular changes noticed during pregnancy may therefore become visible due to the vascular modifications such as vasodilation and proliferation of dermal blood vessels.

Limitations of the present study is the relatively low number of included women and the lack of appropriate control groups, which would have facilitated a better statistical analysis of physiological and truly pregnancy-related changes. Additionally, the included studies are heterogeneous, thus not allowing head-to-head comparisons between them. Furthermore, only one study used a control group, but no study displays raw data facilitating a reanalysis, compared or merged.

Importantly, none of the 258 women reported in the studies developed melanoma. Considering a age-standardised incidence for melanoma between 9 and 33 per 100,000 people in the female population (30, 31), even when considering the highest incidence of melanoma, the likelihood of no woman developing a melanoma in our analysis lies at 92.8% (calculated using the binominal distribution, where $(1-33/100000)^{226}=0.928$). In order to accept or reject a hypothetical increase in the incidence of melanoma of 17% (considered based on the increase in mortality from melanoma in pregnant women), a study would have to include between 30,000 and 100,000 women, taking a Bayes factor of at least 3 which is the minimal value for data to be considered substantial using the Jeffrey's scale (30, 32, 33). See Figures 2A, 2B and 2C.

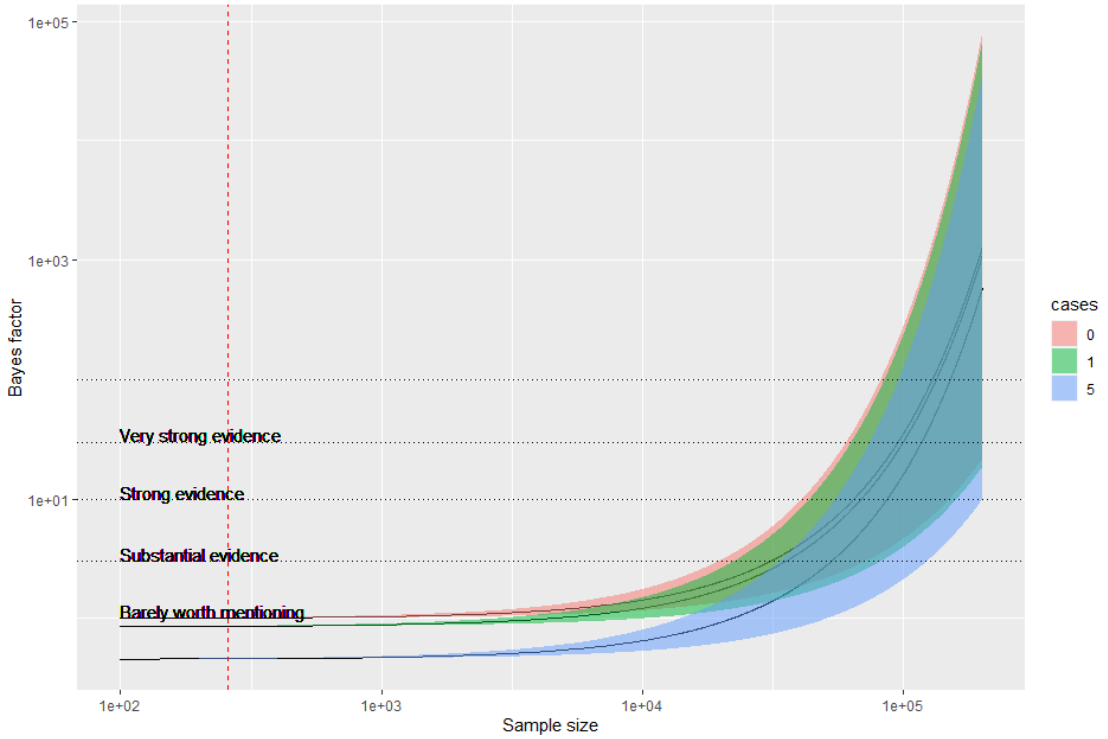

Figure 2A. Sample size calculation. Evidence (as per Bayer factor) versus sample of size needed to prove or disprove an incidence 17% higher, in case 0, 1, or 5 cases of melanoma are eventually diagnosed. An average incidence of 21 per 100,000 people and year in the female population, with error envelopes for incidences between 9 and 33 per 100,000 people and year. The red dashed line shows the evidence for a sample of 226 women.

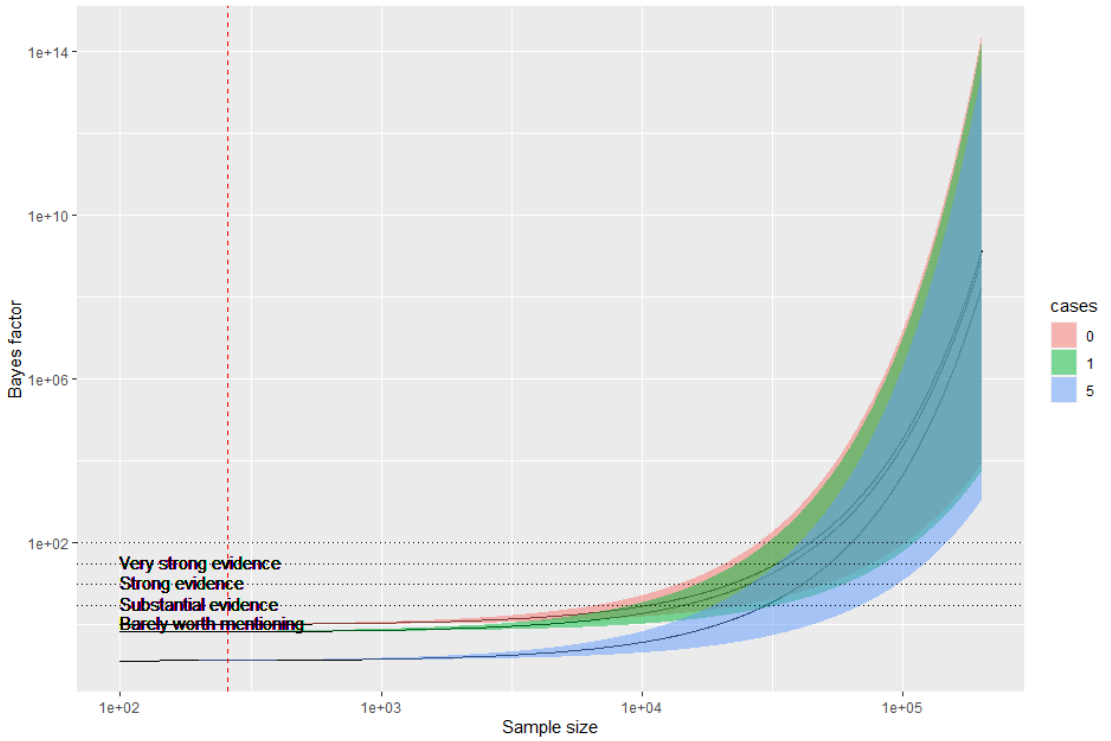

Figure 2B. Sample size calculation for distinguishing a 50% higher melanoma incidence.

Evidence (as per Bayer factor) versus sample of size needed to prove or disprove an incidence 50% higher, in case 0, 1, or 5 cases of melanoma are eventually diagnosed.

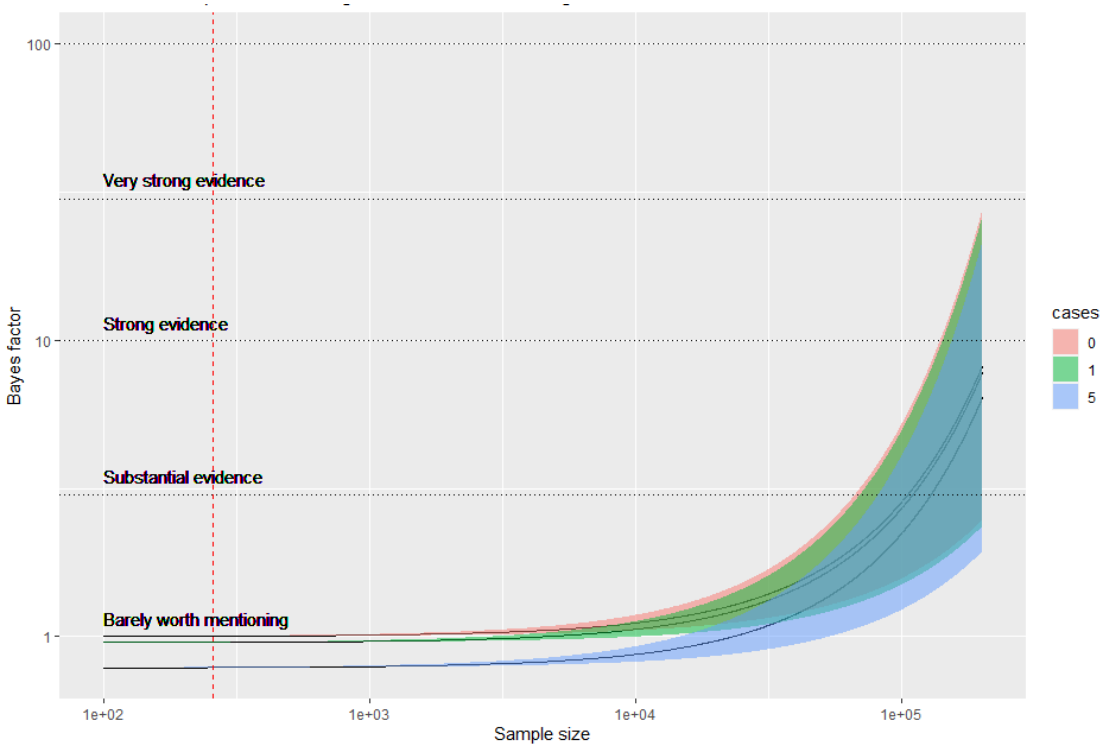

Figure 2C. Sample size calculation for distinguishing a 5% higher melanoma incidence.

Evidence (as per Bayer factor) versus sample of size needed to prove or disprove an incidence 5% higher, in case 0, 1, or 5 cases of melanoma are eventually diagnosed.

Robust studies of dermatoscopic evaluation of naevi in pregnant women are needed to determine high-risk dermatoscopic characteristics which would improve the diagnostic accuracy of benign versus malignant melanocytic lesion in this population.

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8. Appendix

Table A1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	x
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	x
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	x
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	x
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	x
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	x
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	x
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	x
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	x
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	x
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	x
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	x
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	x
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	x
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	x
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	x
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	x
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	x
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	x
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	x
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	x
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	x
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	x
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	x
	23b	Discuss any limitations of the evidence included in the review.	x
	23c	Discuss any limitations of the review processes used.	x
	23d	Discuss implications of the results for practice, policy, and future research.	x
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	x
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	x
Competing interests	26	Declare any competing interests of review authors.	x
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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Table A2. Quality assessment of included studies according to the Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome
Zampino et al, 2006	□□		□
Aktürk et al, 206	□□		□
Rubegni et al, 2006	□□□	□	□□□
Martins-Costa G.M, Bakos R, 2019	□□		□
Gunduz et al, 2003	□□		□
Strumia, 2002	□□		□

Table A3. Risk of bias assessment of included studies according to the Cochrane Risk of Bias Tool

Study	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting
Zampino et al, 2006	no	no	no	no	no	no
Aktürk et al, 206	no	no	no	no	no	no
Rubegni et al, 2006	no	no	no	no	no	no
Martins-Costa G.M, Bakos R, 2019	no	no	no	no	no	no
Gunduz et al, 2003	no	no	no	no	no	yes
Strumia, 2002	no	no	no	no	no	no