An international consensus on the use of asthma biologics in pregnancy

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Uncontrolled asthma is associated with an increased risk of adverse perinatal outcomes. Asthma biologics reduce exacerbation frequency, are steroid sparing, and improve quality of life in people with severe asthma. However, evidence for the use and safety of asthma biologics during pregnancy is scarce, largely because pregnant women were excluded from clinical trials. To help to support clinical teams, we conducted an international modified Delphi study. 141 panellists from 32 countries who were involved in the care of people with severe asthma completed two rounds of online surveys covering key areas surrounding the use of asthma biologics in pregnancy. The results from this international Delphi study emphasise risk versus benefit discussions and shared clinical decision making, with consensus among panellists that asthma biologics can be used during conception and throughout pregnancy, initiated during pregnancy in line with prescribing criteria for non-pregnant people, and initiated or continued during breastfeeding. Collating data through international registries remains essential to inform clinical guidelines.

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Introduction

Asthma is one of the most common pre-existing medical conditions in pregnancy, with a described prevalence in pregnancy of 3·7–8·4%.[1,2] Guidelines on the management of asthma in pregnancy advocate a stepwise approach mirroring that for non-pregnant adults with asthma.[3,4] A substantial body of evidence supports the safety of the most common drug classes used to treat people with asthma during pregnancy, including β_2-agonists and inhaled corticosteroids.[5–7]

Asthma control can change during pregnancy, with 124 (40%) of 308 people in a US prospective cohort reporting worsening control based on daily activity limitation, night-time symptoms, inhaler use, and respiratory symptoms.[8] Uncontrolled asthma and asthma exacerbations are associated with an increased risk of several adverse perinatal outcomes, including an increased risk of low fetal birthweight, preterm delivery, and maternal pre-eclampsia.[9] Increased asthma severity confers the greatest risk of exacerbations, with more than 65% of women with severe asthma having exacerbations requiring treatment during pregnancy.[10] In addition to the risks associated with exacerbations, oral corticosteroids, which are the standard of care for treatment of exacerbations, are associated with numerous short-term and long-term side-effects.[11]

Since 2003, several biologics have become available for people with severe asthma (table 1). Clinical trials have consistently shown that these biologics reduce exacerbation frequency, are steroid sparing, and improve quality of life in people with severe asthma.[12] However, data on the safety and efficacy of asthma biologics during pregnancy is scarce, largely because pregnant people were excluded from the clinical trials. Early pharmacovigilance data and published case series[13–18] do not report an association between asthma biologic use and adverse outcomes during or after pregnancy. Using cases submitted to the WHO pharmacovigilance database, Khamisy-Farah and colleagues reported no association between the use of dupilumab during pregnancy in women with atopic dermatitis and any adverse drug reactions, but the authors acknowledged that further studies are needed because only 36 of 37 848 reports submitted were related to the use of dupilumab during pregnancy.[19]

The EXPECT registry was established in 2006 to evaluate perinatal outcomes in women exposed to omalizumab during pregnancy.[20] No increased risk of preterm delivery or major congenital anomalies was reported compared with a disease-matched unexposed

Key messages

Rationale and approach

Asthma is one of the commonest pre-existing medical conditions in pregnancy, with uncontrolled disease associated with an increased risk of several adverse perinatal outcomes. Asthma biologics improve asthma control, reduce exacerbations, and are steroid sparing; however, data on their safety and efficacy during pregnancy is limited due to the exclusion of pregnant people from clinical trials. For this reason, there is an absence of clear guidance and substantial variation in clinical practice. To help support clinical teams, we carried out a Delphi study on the use of asthma biologics in pregnancy. 141 experts (ie, pulmonary physicians, allergists, specialist nurses, pharmacists, and obstetricians) from 32 countries participated in two rounds of a web-based Delphi process.

Findings

Panellists gave consensus for 34 of 69 statements on the use of asthma biologics during conception, pregnancy, and breastfeeding. Namely, the importance of risk versus benefit discussions with patients and shared decision making was emphasised and there was agreement that asthma biologics do not need to be stopped while patients are trying to conceive; asthma biologics can be continued throughout pregnancy; biologics can be initiated during pregnancy in line with national prescribing criteria and especially in people with frequent exacerbations (ie, four or more in a 12-month period); asthma-related admissions to hospital or an intensive care unit and the presence of steroid side-effects should lower the threshold for initiating the biologic during pregnancy; and asthma biologics can be initiated and continued while breastfeeding.

Future directions and implications

The consensus agreements from this international Delphi provide support for clinicians and people wanting to use asthma biologics in pregnancy and should help to improve asthma-related maternal outcomes during pregnancy and reduce variation in care. Collating data through international registries remains crucial to inform clinical guidelines and practice.

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	FDA licence	EMA licence	MHRA licence	NICE approval and licence	IgG subtype	Mechanism of action
Omalizumab	June 6, 2003	Oct 25, 2005	Approved via EMA	Severe persistent allergic asthma: November, 2007	IgG1	Anti-IgE; binds to IgE and prevents it from binding to the high-affinity IgE receptor
Mepolizumab	Nov 4, 2015	Dec 2, 2015	Approved via EMA	Severe persistent allergic asthma: April, 2016 (updated January, 2020)	IgG1κ	Anti-IL-5; binds directly to IL-5 to prevent its link with IL-5RA
Reslizumab	March 23, 2016	Aug 15, 2016	Approved via EMA	Severe eosinophilic asthma: October, 2017	IgG4	Anti-IL-5; binds directly to IL-5 to prevent its link with IL-5RA
Benralizumab	Nov 14, 2017	Jan 8, 2018	Approved via EMA	Severe eosinophilic asthma: March, 2019	IgG1κ	Binds to the α subunit of IL-5R on eosinophils and basophils, thus preventing IL-5 binding and amplifying the antibody-dependent cellular cytotoxicity function of these cells by activating natural killer cells to perform apoptosis
Dupilumab	Oct 19, 2018	May 7, 2019	Approved via EMA	Severe asthma with type 2 inflammation: December, 2021	IgG4	Anti-IL-4RA; inhibits signalling of IL-4 and IL-13 cytokines
Tezepelumab	Dec 17, 2021	Sept 19, 2022	Sept 23, 2022	Severe asthma: April, 2023	IgG2λ	Anti-TSLP; binds to TSLP so prevents its link to its cognate receptor CRLF2

Dates shown reflect the licence for asthma. FDA=US Food and Drug Administration. EMA=European Medicines Agency. MHRA=Medicines and Healthcare Products Regulatory Agency. NICE=National Institute for Health and Care Excellence.

Table 1: **Summary of asthma biologics**

cohort.[21] Registries involving pregnant women exposed to the other biologics will be essential to collate data and inform clinical guidelines. Specifically, registries involving mepolizumab and dupilumab in the USA and Canada are ongoing and results are not expected until at least 2026 (NCT04173442, NCT04287621).[22,23] The US registry investigating benralizumab exposure in pregnancy was terminated prematurely due to recruitment challenges (NCT03794999).

Given the paucity of evidence and guidance in this area, we aimed to gain an international consensus on the use of asthma biologics in pregnancy using a modified Delphi method to support clinicians and aid shared decision-making processes with people with severe asthma.

Methods

We used a modified Delphi process consisting of two rounds to assess consensus (figure 1). The modified Delphi method allows the creation and adjustment of items between iterative rounds of questionnaires based on feedback received.[24] A steering committee comprising seven experts (ie, five severe asthma physicians, an obstetric physician, and a consultant pharmacist) developed initial questions and statements based on their clinical expertise and literature review. These statements covered five key areas surrounding the use of asthma biologics in pregnancy: conception, delivery of asthma care during pregnancy, initiation of asthma biologic treatments in pregnancy, continuation of asthma biologic treatments in pregnancy, and postpartum care.

Literature review

We searched PubMed using the Medical Subject Heading (MeSH) terms "pregnancy", "asthma", "severe asthma", "asthma biologics", "safety", "placental transport", and "Delphi methodology" to identify studies published in English from Jan 1, 1994, to April 1, 2024. These MeSH terms were linked by use of Boolean operators. Titles were then filtered by article type, prioritising systematic reviews, randomised controlled trials, and observational studies where available. Identified case reports, observational studies, and review articles were searched to identify any further relevant studies. The literature review performed was used to aid the steering committee in the development of the Delphi surveys.

Delphi participants

The steering group sent e-mail invitations to health-care professionals who were active members of international and national severe asthma registries (ie, the International Severe Asthma Registry; the Severe Heterogeneous Asthma Research Collaboration, Patient-centred; and the UK Severe Asthma Registry) to participate in the Delphi study.[25–27] The UK MacDonald Obstetric Medicine Society members were also invited to participate. Panellists who responded to the invite were deemed eligible to participate if they answered "yes" to the screening question: "Do you look after patients on asthma biologics?" Both prescribers and non-prescribers of asthma biologics were invited to participate to reflect everyday clinical practice where the decision to initiate treatment is often made by a multidisciplinary team. In addition to the questions and statements in round 1, panellists completed seven questions on their background demographics and experience in the use of asthma biologics (table 2). Participants were made aware at the start of the first survey that e-mail addresses submitted would be collected and held to facilitate targeted invites

for subsequent rounds. Participants were given the option to disclose their names after data collection and analysis had been completed to allow participant acknowledgment in any publications arising from the study.

Patients were not involved in the Delphi study because statements largely related to prescribing criteria and responses required an understanding of the various biologics available and an in-depth knowledge of the risk–benefit evaluation that clinicians do when considering treating pregnant people. Additionally, the steering committee felt that the co-ordination of the timely participation of pregnant people with severe asthma would be challenging.

Delphi statements

The Delphi process consisted of two rounds, in which surveys comprising the agreed questions and statements were sent to panellists in the form of an email hyperlink that directed panellists to complete the survey on a web-based electronic platform using Google Forms. The full Delphi surveys are shown in the appendix (pp 3–18). Other than email addresses, no other identifiable information was collected from panellists throughout the Delphi process and responses were anonymous. The email addresses were held centrally by two of the authors responsible for project administration and used to send invitations to complete round 2. The surveys asked panellists multiple choice and open-ended questions and to rank responses to statements using a five-point Likert scale (ie, "strongly agree", "agree", "don't know", "disagree", and "strongly disagree"). To progress through the survey, panellists were mandated to provide an answer for each statement or question. An optional free-text comment box was available for panellists to use after each question or statement.

In round 1, 44 statements and eight questions were submitted. The questions were included to gain information from panellists about their responses and inform subsequent Delphi rounds (full Delphi surveys can be found in the appendix pp 3–18). In round 2, 25 statements were submitted. Two new statements were introduced in round 2 based on feedback from round 1, one statement was removed and the remaining statements were revised statements from the first round. Summary results were provided to panellists from round 1 to facilitate informed decision making in subsequent rounds. Panellists were given 3 weeks to respond to each Delphi round, with reminders sent during this time where necessary.

Statistical analysis

Consensus agreement was predetermined by the steering committee as 75% or more of panellists responding "agree" or "strongly agree". A threshold of 75% or more is a widely accepted cutoff, with strong agreement set at 90% or more.[28] After round 1, if a statement achieved less than 75% consensus it was reviewed and resubmitted in the subsequent Delphi round based on the feedback received. If less than 50% consensus was achieved, the statement was removed, except where comments indicated ambiguity or misunderstanding. Once each Delphi round was complete, the data were automatically exported from Google Forms into Microsoft Excel for analysis. The level of agreement across all questions was automatically analysed by Google Forms, but the steering committee were also able to perform additional analyses, including means and percentages for demographic data entered.

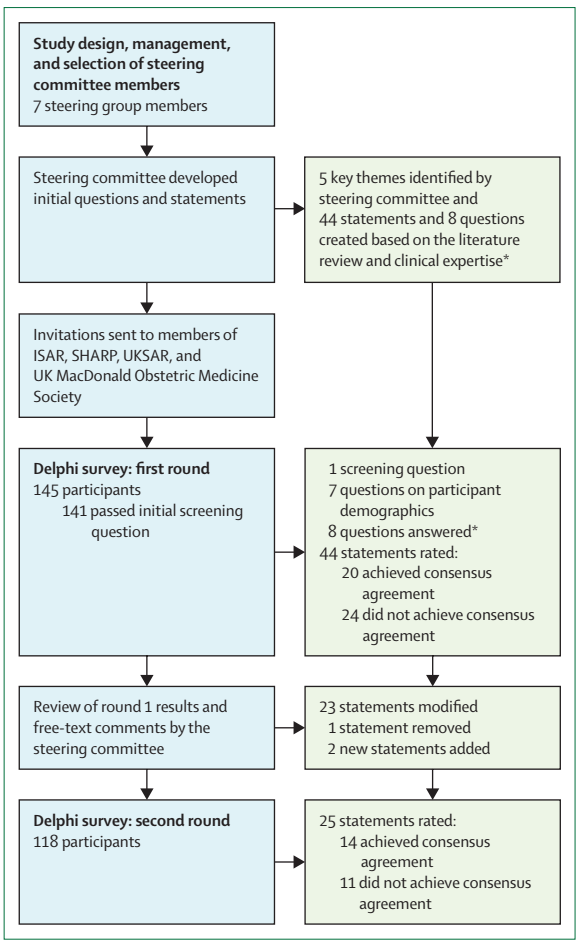

Figure 1: **Overview of consensus development process and Delphi study participation**

The study design, management, and selection of the steering committee was initiated by JN and HR and agreed by all co-authors. Health-care professionals who were active members of international and national severe asthma registries were invited to participate in the Delphi as well as members of the UK MacDonald Obstetric Medicine Society. The Delphi surveys are listed in full in the appendix (pp 3–18). ISAR=International Severe Asthma Registry. SHARP=Severe Heterogenous Asthma Research Collaboration, Patient-centred. UKSAR=UK Severe Asthma Registry. *In addition to statements, eight questions were submitted in round 1 to gain additional information from participants and inform further Delphi rounds.

Results

The Delphi process ran from April 18 to July 10, 2023. 145 individuals completed the screening questions in

See Online for appendix

	Panellists (n=141)
Occupation	
Respiratory physician	102 (72%)
Allergist	12 (9%)
Obstetrician with specialist interest in maternal medicine, including asthma	2 (1%)
Obstetric physician	2 (1%)
Pharmacist	10 (7%)
Specialist nurse	12 (9%)
Other allied health-care professional	1 (1%)
Time qualified	
≤5 years	20 (14%)
6–10 years	22 (16%)
11–20 years	45 (32%)
>20 years	54 (38%)
Country of work	
Australia	11 (8%)
Belgium	2 (1%)
Bulgaria	1 (1%)
Canada	2 (1%)
Colombia	3 (2%)
Denmark	3 (2%)
Estonia	1 (1%)
Finland	1 (1%)
France	12 (9%)
Greece	2 (1%)
Hungary	1 (1%)
Iceland	1 (1%)
Ireland	3 (2%)
Italy	5 (4%)
Lithuania	2 (1%)
Mexico	3 (2%)
Netherlands	2 (1%)
New Zealand	3 (2%)
Norway	1 (1%)
Portugal	2 (1%)
Romania	1 (1%)
Russia	1 (1%)
Saudi Arabia	2 (1%)
Serbia	2 (1%)
Singapore	1 (1%)
Slovenia	1 (1%)
Sweden	2 (1%)
Switzerland	1 (1%)
Taiwan	1 (1%)
Turkey	1 (1%)
UK	62 (44%)
USA	5 (4%)

(Table 2 continues on next page)

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	Panellists (n=141)
Prescription of asthma biologics	
Prescribers	120 (85%)
Non-prescribers	21 (15%)
Current number of people cared for who are on asthma biologics	
None	2 (1%)
≤25	21 (15%)
26–50	19 (13%)
>50	99 (70%)
Participation on a severe asthma advisory board or national or international working group in the past 5 years	
Yes	106 (75%)
No	35 (25%)
Number of severe asthma publications authored in the past 5 years	
None	29 (21%)
1–10	63 (45%)
11–30	29 (21%)
>30	20 (14%)

Data are n (%).

Table 2: **Panellist characteristics of those who participated the Delphi study**

round 1 of the Delphi process, with four people excluded at the point of screening. 141 panellists were used for round 1 (appendix pp 20–23). Of these 141 participants, 118 individuals completed round 2, giving a panellist attrition rate of 16·3% (23 panellists). Panellists were mostly respiratory physicians (table 2), but also included allergists, obstetricians with a specialist interest in maternal medicine, obstetric physicians, pharmacists, specialist nurses, and a midwife. Panellists worked across 32 countries (table 2).

In terms of clinical experience, 121 (86%) of 141 panellists had been qualified for more than 5 years in their current job role and most were prescribers of asthma biologics (table 2). Most panellists had participated in a severe asthma advisory board or national or international working group related to asthma in the past 5 years and 112 (79%) had at least one peer-reviewed publication on severe asthma within the past 5 years.

Statements that reached consensus (figure 2) were used to generate a series of consensus themes for clinicians on the use of asthma biologics in pregnancy (figure 3). Comments received are listed in the appendix (pp 24–50) with a full breakdown of responses in (appendix pp 51–56).

Conception

The proportion of panellists who agreed that, with regard to conception (unassisted and assisted), there is no signal of harm associated with the use of asthma biologics was just below the predefined consensus threshold (figure 2). Consistently, panellists commented that there was insufficient evidence in this area and suggested a difference between omalizumab and other asthma biologics due to having more experience in the use of omalizumab during pregnancy, perhaps extending from the EXPECT registry.[21] In view of this

Delphi statement consensus

Reached consensus agreement threshold (ie, ≥75% agreement) Did not reach consensus agreement threshold (ie, 50–74% agreement) Reached criteria for exclusion (ie, <50% agreement)

	Round 1 (n=141)	Round 2 (n=118)
Conception		
With regard to conception (unassisted and assisted), there is no signal of harm associated with the use of asthma biologics*	No consensus (105 [74·5%])	NA
Based on current experience, with regard to conception (unassisted and assisted), there is no signal of harm associated with the use of asthma biologics	NA	Consensus agreement (108 [91·5%])
All patients who are of child-bearing age should have documented discussions with their specialist team about the use of asthma biologics in pregnancy at the point of commencing treatment	Consensus agreement (129 [91·5%])	NA
If clinically indicated and agreed by the patient, asthma biologics can be initiated in people trying to conceive	Consensus agreement (119 [84·4%])	NA
If clinically indicated and agreed by the patient, asthma biologics can be continued in people trying to conceive	Consensus agreement (133 [94·3%])	NA
Care delivery		
All people with severe asthma who become pregnant should have a review by a trained asthma health-care professional within 12 weeks (ie, in the first trimester) of becoming pregnant	Consensus agreement (133 [94·3%])	NA
Pregnant people with severe asthma should have a named respiratory consultant and consultant obstetrician throughout their pregnancy	Consensus agreement (130 [92·2%])	NA
An obstetrician or obstetric physician should be involved in discussions of pregnant patients on asthma biologics	Consensus agreement (119 [84·4%])	NA
Pregnant patients on asthma biologics should be recorded on a national or international registry	Consensus agreement (133 [94·3%])	NA
During pregnancy, administration of asthma biologics should occur in the hospital or clinic setting (rather than home setting)†	No consensus (31 [22·0%])	NA
During pregnancy, the place of administration of asthma biologics (ie, home or hospital or clinical setting) does not need to change	NA	Consensus agreement (92 [78·0%])
Initiation of asthma biologic treatments during pregnancy		
All patients receiving an asthma biologic during pregnancy should have documented discussions with their specialist team about the use of asthma biologics in pregnancy	Consensus agreement (140 [99·3%])	NA
If clinically indicated and agreed by the patient, people with severe asthma should be initiated on asthma biologic therapy during pregnancy*	No consensus (83 [58·9%])	NA
Assuming the patient is in agreement, and the risks and benefits have been discussed, if clinically indicated people with severe asthma can be initiated on asthma biologic therapy during pregnancy	NA	Consensus agreement (105 [89·0%])
Assuming the patient is in agreement, and the risks and benefits have been discussed, I would start an asthma biologic in someone who is pregnant if they met national prescribing criteria in line with criteria for non-pregnant patients	NA	Consensus agreement (94 [79·7%])
A hospital admission due to an asthma exacerbation would lower my threshold for initiating an asthma biologic during pregnancy	Consensus agreement (111 [78·7%])	NA
An admission to intensive care due to an asthma exacerbation within the last 12 months would lower my threshold for initiating an asthma biologic during pregnancy	Consensus agreement (131 [92·9%])	NA
An admission to intensive care due to an asthma exacerbation within the last 10 years would lower my threshold for initiating an asthma biologic during pregnancy‡	No consensus (64 [45·4%])	NA
Risk factors for gestational diabetes or the development of gestational diabetes would lower my threshold for starting an asthma biologic during pregnancy*	No consensus (99 [70·2%])	NA
The presence of other steroid side-effects (eg, osteoporosis) would lower my threshold for starting an asthma biologic in pregnancy*	No consensus (97 [68·8%])	NA
The presence of one or more steroid-related side-effects would lower my threshold for starting an asthma biologic; this would include (but is not limited to) gestational diabetes (or risk of gestational diabetes), reduced bone density, and steroid-induced psychosis	NA	Consensus agreement (109 [92·4%])
The presence of two or more steroid-related side-effects would lower my threshold for starting an asthma biologic; this would include (but is not limited to) gestational diabetes (or risk of gestational diabetes), reduced bone density, and steroid-induced psychosis	NA	Consensus agreement (113 [95·8%])

(Figure 2 continues on next page)

Delphi statement consensus

Reached consensus agreement threshold (ie, ≥75% agreement) | Did not reach consensus agreement threshold (ie, 50–74% agreement) | Reached criteria for exclusion (ie, <50% agreement)

Continuation of asthma biologic treatments in pregnancy		
If a pregnant person's asthma is stable on the following asthma biologic (commenced before conception), this can be continued throughout pregnancy including the third trimester (options given: yes—if we agree benefits outweigh potential risks, yes—but only if they have a history of life-threatening exacerbations before starting an asthma biologic, no—stop as soon as we are made aware of the pregnancy, and no—stop before the third trimester)§		
Omalizumab	Consensus agreement (136 [96·5%])	NA
Mepolizumab	Consensus agreement (124 [87·9%])	NA
Benralizumab	Consensus agreement (118 [83·7%])	NA
Reslizumab	Consensus agreement (108 [76·6%])	NA
Dupilumab	Consensus agreement (110 [78·0%])	NA
Tezepelumab	No consensus (91 [64·5%])	NA
Postpartum care		
Patients can receive the first dose of their asthma biologic after birth at home if they have already received three or more injections and home-care facilities are available	Consensus agreement (126 [89·4%])	NA
If stopped for conception or during pregnancy (either through patient choice or following professional advice), asthma biologics can be restarted as soon as possible after birth¶	NA	Consensus agreement (109 [92·4%])
Asthma biologics can be initiated or continued while breastfeeding*	No consensus (102 [72·3%])	NA
Assuming the patient is in agreement, and the risks and benefits have been discussed, asthma biologics can be initiated while breastfeeding	NA	Consensus agreement (115 [97·5%])
Assuming the patient is in agreement, and the risks and benefits have been discussed, asthma biologics can be continued while breastfeeding	NA	Consensus agreement (114 [96·6%])
I advise patients who have received an asthma biologic in pregnancy that this might affect the timings of infant vaccination schedules¶	NA	No consensus (16 [13·6%])
After birth, how long do you recommend avoiding live-attenuated vaccinations for the infant if the mother received this asthma biologic (options given: omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab, and tezepelumab) during pregnancy and it was stopped before the end of the second trimester (options given: no need to avoid—continue with the normal recommendations for infant vaccinations, avoid live-attenuated vaccinations for the first 6 months of life, or don't know)?*	No consensus achieved for any of the options with any of the biologics‖	NA
After birth, how long do you recommend avoiding live-attenuated vaccinations for the infant for if the mother received this asthma biologic (options given: omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab, and tezepelumab) throughout the pregnancy including the third trimester (options given: no need to avoid—continue with the normal recommendations for infant vaccinations, avoid live-attenuated vaccinations for the first 6 months of life, or don't know)?*	No consensus achieved for any of the options with any of the biologics‖	NA
After birth, you should avoid live-attenuated vaccinations for the infant if the mother received this asthma biologic during pregnancy		
Omalizumab	NA	No consensus (78 [66·1%])
Mepolizumab	NA	No consensus (72 [61·0%])
Benralizumab	NA	No consensus (70 [59·3%])
Reslizumab	NA	No consensus (62 [52·5%])
Dupilumab	NA	No consensus (57 [48·3%])
Tezepelumab	NA	No consensus (47 [39·8%])

(Figure 2 continues on next page)

fact, the statement was resubmitted in round 2 with the addition of the phrase "based on current experience", and consensus was reached between panellists that, with regard to conception, based on current experience, there is no signal of harm associated with the use of asthma biologics. Consensus was reached for all other statements in this category in round 1 (figure 2). Notably, panellists felt there needed to be a balance between discussing the risks and benefits of biologics in people of childbearing age and with not overburdening patients with information (appendix p 28).

Delphi statement consensus

Reached consensus agreement threshold (ie, ≥75% agreement) | Did not reach consensus agreement threshold (ie, 50–74% agreement) | Reached criteria for exclusion (ie, <50% agreement)

After birth, there is no need to avoid inactivated vaccinations for the infant if the mother received the following asthma biologic during pregnancy		
Omalizumab	NA	Consensus agreement (101 [85·6%])
Mepolizumab	NA	Consensus agreement (100 [84·7%])
Benralizumab	NA	Consensus agreement (99 [83·9%])
Reslizumab	NA	Consensus agreement (91 [77·1%])
Dupilumab	NA	Consensus agreement (98 [83·0%])
Tezepelumab	NA	No consensus (88 [74·6%])

Figure 2: **Summary of responses to statements in Delphi rounds 1 and 2**
58 of 69 statements are shown, with the remaining 11 statements forming scenarios and their results displayed in figure 4. Delphi statements were classified as reaching consensus agreement threshold if there was more than or equal to 75% agreement. Delphi statements were classified as not reaching consensus threshold if there was 50–74% agreement. Delphi statements reached the criteria for exclusion if there was less than 50% agreement. NA=not applicable. *Round 1 statements modified and resubmitted in round 2. †The only statement to meet exclusion criteria of a consensus of less than 50% but was resubmitted in round 2 based on feedback received. ‡Statement removed and not resubmitted in round 2. §Results are shown for panellists who answered with the options "yes—if we agree benefits outweigh potential risks" or "yes—but only if they have a history of life-threatening exacerbations before starting an asthma biologic". ¶New statements added to round 2. ||A full breakdown of responses for these statements are shown in the appendix (p 55).

Care delivery

There was strong agreement that all people with severe asthma who become pregnant should have a review by a trained asthma health-care professional within 12 weeks (ie, in the first trimester) of becoming pregnant (figure 2). However, the comments received emphasised that review at this stage is not always possible with later presentation to clinical services due to delay in pregnancy diagnosis or in notifying severe asthma teams (appendix p 24). There was a preference for shared decision making with strong agreement that a pregnant person with severe asthma should have both a named respiratory and obstetric consultant throughout their pregnancy and panellists also agreeing that an obstetrician or obstetric physician should be involved in the discussions of pregnant people receiving asthma biologics. There was strong agreement that pregnant people on asthma biologics should be recorded on a national or international registry, with panellists showing a willingness to participate in such registries.

In round 1, only a minority of panellists agreed that administration of asthma biologics should occur only in the hospital or clinic setting during pregnancy. Panellists commented on not being able to see any additional benefit from this requirement and that switching to hospital administration could be inconvenient in terms of distance and associated travel costs, which might reduce adherence (appendix pp 26–27). When resubmitted in round 2 as "the place of administration of asthma biologics does not need to change", consensus was achieved.

The initiation of asthma biologics in pregnancy

Nearly all panellists felt that discussions between people receiving an asthma biologic during pregnancy and their specialist team about the role, benefits, and unknowns of the use of asthma biologics in pregnancy should be documented.

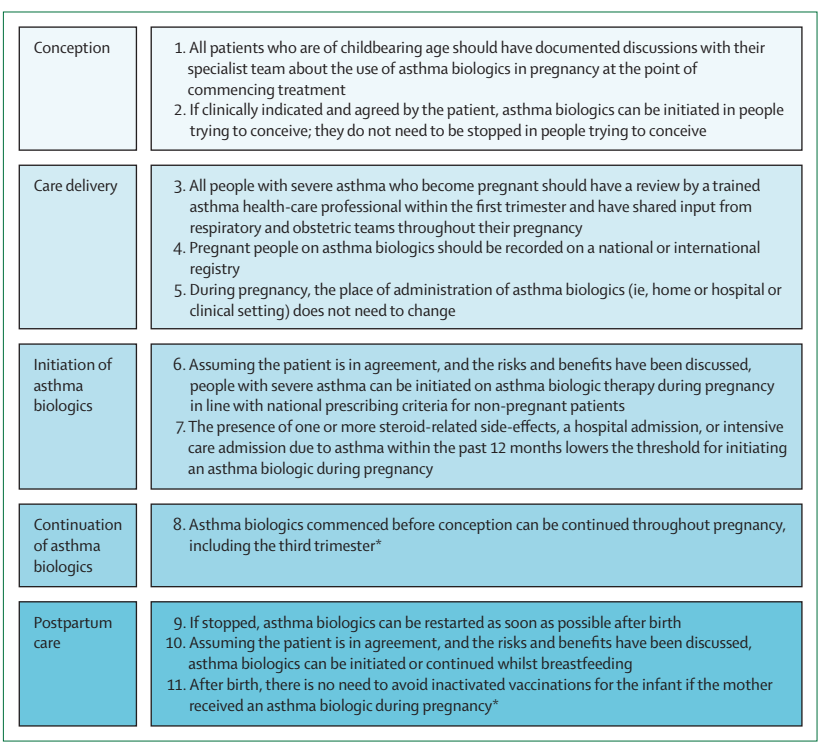

Figure 3: **Summary of consensus themes on the use of asthma biologics in pregnancy**
*With the exception of tezepelumab, possibly due to limited experience at the time of the Delphi study.

In round 1, more than half of panellists agreed that an asthma biologic should be initiated during pregnancy in someone with severe asthma. Key themes in the statement feedback were that this decision was dependent on an individualised assessment of risk versus benefit by the patient. The statement was reworded for round 2 to reflect these comments and, subsequently, panellists reached a consensus that an asthma biologic could be initiated during pregnancy (figure 2). Those

who strongly disagreed or disagreed were asked to elaborate on their hesitancy to use an asthma biologic during pregnancy. Concerns about potential fetal harm during pregnancy and a scarcity of registry data and national guidelines were identified as key issues (appendix p 19). Distinctions were also made between the different biologics and initiating versus continuing a treatment.

To ascertain criteria that clinicians might consider for starting an asthma biologic for a pregnant person, panellists were given scenarios that included the number of exacerbations or the dose of maintenance oral corticosteroids at which they would start an asthma biologic in pregnancy. The exact scenarios presented to participants are shown in the appendix (pp 8–10). There was clear consensus that biologics should be initiated in pregnant people who had four or more exacerbations requiring oral corticosteroids in the previous 12 months or were on maintenance oral corticosteroids of 10 mg/day or more (figure 4). Many panellists commented on the need to ensure inhaler technique and adherence had been optimised first as done for non-pregnant patients before commencing an asthma biologic (appendix p 32). Some of the responses mentioned national differences in prescribing and reimbursement criteria; therefore, in round 2, panellists were asked whether they would prescribe an asthma biologic in pregnancy in line with criteria for a non-pregnant person and consensus agreement was reached (figure 2).

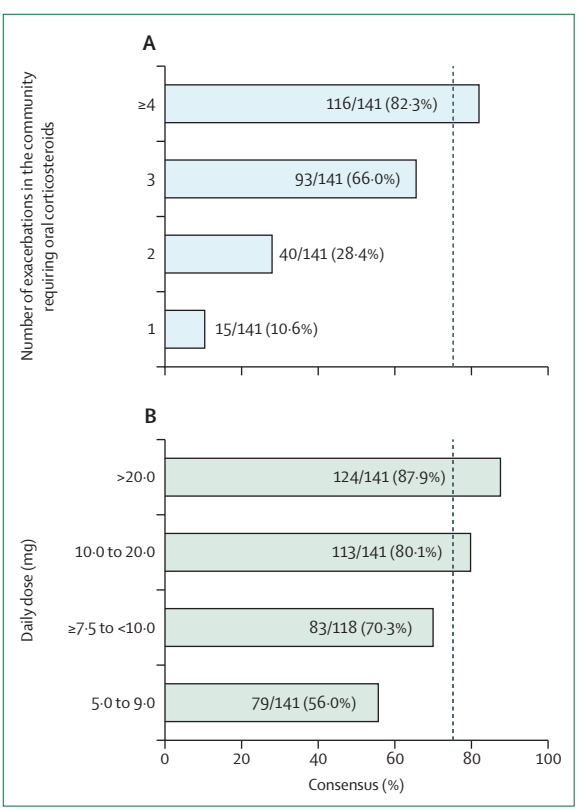

Figure 4: **Levels of consensus achieved for criteria for initiating an asthma biologic during pregnancy**
To establish consensus on these criteria, the following statements were included in the Delphi survey: "Assume the patient is adherent to appropriate high-dose inhaled corticosteroids, that their comorbidities have been addressed, and their biomarkers (ie, blood eosinophil count, fractional exhaled nitric oxide, and total IgE) are raised. In which of these scenarios would you consider starting an asthma biologic in someone who is pregnant?" (A) Number of exacerbations requiring oral corticosteroids. (B) Daily dose of maintenance oral corticosteroids. The dashed line indicates the predefined level of consensus (ie, ≥75%).

Consensus was reached between panellists that hospital admissions and an intensive care unit admission within the last 12 months lowered the threshold for initiating an asthma biologic during pregnancy. The panellists did not reach a consensus agreement that an intensive care unit admission in the past 10 years lowered the threshold, perhaps emphasising that more recent asthma control before conception is an important factor in decision making. Panellists were in strong agreement that the presence of one or more steroid-related side-effects, such as gestational diabetes, reduced bone density, and steroid-induced psychosis, also lowered the threshold for initiating asthma biologic treatment during pregnancy.

Continuation of asthma biologics in pregnancy

Consensus was achieved regarding continuing asthma biologics throughout pregnancy (assuming the pregnant person's asthma is stable), including the third trimester. Less than 6·5% of panellists, regardless of the asthma biologic, recommended stopping an asthma biologic before the third trimester (appendix p 55).

The strength of agreement achieved was related to years of clinical experience with each asthma biologic, with the first FDA approved biologic, omalizumab, achieving the strongest level of agreement. Panellists felt least comfortable with continuing tezepelumab during pregnancy. Tezepelumab was the only asthma biologic to not achieve the predefined consensus threshold for continuation, which likely reflects that tezepelumab is the latest biologic to receive FDA approval, with many panellists commenting that tezepelumab has yet to be made available in their country.

Postpartum care

In round 1, we asked when panellists advise restarting an asthma biologic after birth, with 111 (78·7%) of 141 responding "as soon as possible" or "not applicable as I would not recommend stopping an asthma biologic for conception or during pregnancy" (appendix p 19). Subsequently, we formed a round 2 statement where strong agreement was met that, when stopped (either through patient choice or professional advice), an asthma biologic can be restarted as soon as possible after birth, with panellists also agreeing that the place of administration of asthma biologics does not need to change during pregnancy.

During round 1, panellists did not come to a consensus on asthma biologics being initiated or continued during

breastfeeding. Feedback from panellists was mixed, with many commenting on the absence of available data in this area, others emphasising the need for joint decision making with the patient, and some commenting on the oral bioavailability of the biologics, with their large molecular size making it unlikely that they would be detected in breast milk or absorbed orally in the infant. One panellist emphasised the risk distinction between initiating versus continuing a biologic. Based on this feedback, in round 2, the statement was split into continuing versus initiating an asthma biologic and a stem of "assuming the patient is in agreement, and the risks and benefits have been discussed" was added. Both statements concerning asthma biologics in breastfeeding achieved more than 95% agreement in round 2 (figure 2).

Finally, in both round 1 and round 2, agreement was not reached on statements concerning changes to infant live-attenuated vaccination schedules when the mother has received an asthma biologic during pregnancy (figure 2; appendix pp 55–56). These statements were included because rheumatology guidelines advocate delaying live-attenuated vaccines in the infant for 6 months when the mother has received an anti-TNF biologic during pregnancy.[29] During round 1, statements focused on the timing of live-attenuated vaccinations for the infant and whether the timing varied depending on when the mother stopped the asthma biologic (ie, before the third trimester) or continued throughout pregnancy. Like previous findings in this Delphi, the trimester of asthma biologic administration did not seem to factor into panellists' decisions, with consensus not being achieved for any statements. When resubmitted in round 2, the trimester component was removed and panellists were asked whether live-attenuated and inactive vaccinations should be delayed in infants when the mother had received an asthma biologic during pregnancy. Again, no agreement was reached regarding live-attenuated vaccinations. However, an agreement was reached for all asthma biologics (except tezepelumab) that there is no need to delay inactivated vaccinations for the infant. Only a small proportion of panellists agreed that they would advise patients who had received an asthma biologic in pregnancy that timings of vaccinations for their infant might need to change (appendix p 53). The lack of consistent consensus regarding live-attenuated vaccination schedules for infants likely reflects insufficient evidence and understanding in this area.

Discussion

This Delphi study gathered an international consensus on the use of asthma biologics in pregnancy (figure 3). Namely, the panellists reached consensus that asthma biologics do not need to be stopped while patients are trying to conceive; that asthma biologics can be used throughout pregnancy; that asthma biologics can be initiated during pregnancy in line with national prescribing criteria for non-pregnant people, especially in people with frequent exacerbations (ie, four or more exacerbations in a 12-month period); that asthma-related admissions to hospital or admissions to intensive care units within the past 12 months and the presence of steroid side-effects can lower the threshold for initiating biologics during pregnancy; that asthma biologics can be initiated and continued while breastfeeding; and that shared decision making should underpin all decisions regarding biologic use during conception, pregnancy, and breastfeeding. Key themes from the consensus statements were the importance of risk versus benefit discussions and shared decision making with people with asthma, a multidisciplinary team approach, and the need to develop international registries to inform clinical guidelines.

Panellists did not recommend stopping any of the asthma biologics before the third trimester, provided the biologic was helping to maintain asthma stability. Although this result reflects the recognition that good asthma control is important during pregnancy, it was unexpected. With little availability of evidence on the safety of asthma biologics in pregnancy, much of the knowledgebase extends from other clinical specialties, such as rheumatology, for which there is more experience in the use of biologics during pregnancy, often with trimester specific administration guidance.[29]

The asthma biologics are all IgG subclasses (table 1), with IgG and IgA being the only antibodies to show placental transfer from mother to fetus.[30] Early in pregnancy, IgG is transported by passive diffusion, with insignificant amounts reaching the fetus.[30] Fetal IgG concentrations in blood samples obtained by cordocentesis were 5–10% that of the mother at 17–22 weeks gestation.[31] Later in pregnancy, IgG antibodies are actively transported across the placenta, with the rate of transport dependent on the IgG subclass Fc portion and efficacy as follows: IgG1>IgG4>IgG3>IgG2.[32] This process results in much higher or similar IgG cord blood concentrations than that of the maternal circulation during the third trimester.[30] Consequently, many specialties advocate stopping maternal administration of biologics before or at the beginning of the third trimester (ie, 26–30 weeks of gestation), largely due concerns about the immunosuppressive effects of the anti-TNF biologics.[29] 2023 Guidelines from the British Society of Rheumatology advise different gestation stopping points based on the individual biologic prescribed and the maternal disease severity.[29] However, biologics targeting the type 2 inflammatory pathway in asthma are not broadly immunosuppressive and are well tolerated in real-world populations without increased risk of or susceptibility to severe infection in adults or children or after exposure during pregnancy.

Studies in non-human primates suggest that the eosinophil-depleting effect of benralizumab does not seem to

affect infant development.[14,33] In humans, five case reports have been published detailing the use of benralizumab throughout pregnancy (four in women with asthma and one in a woman with hypereosinophilic syndrome), adding weight to the suggestion that eosinophil depletion does not appear to affect infant development.[14,16] In one of these cases, detectable blood eosinophils were reported by 8 weeks in the infant and, in another case, no adverse effects on infant development were reported despite the infant eosinophil count remaining undetectable for the first 7 months of life. The lack of a harmful signal reported to date in infants exposed to asthma biologics in utero, in addition to the risks of uncontrolled asthma in pregnancy, might be why less than 6·5% of panellists would stop an asthma biologic before the third trimester (appendix p 55).

Panellists reached a consensus agreement that four or more exacerbations in the previous 12 months were the threshold at which biologics should be initiated during pregnancy. 62 (44%) of 141 panellists were based in the UK, and UK national prescribing criteria, which mandates three exacerbations in the 12 months before biologic prescribing, might have influenced their responses. However, the lower threshold of three exacerbations did not achieve consensus, and it is likely that the higher threshold of four exacerbations reflects a combination of the international differences in prescribing criteria[34] and hesitancy to initiate biologics during pregnancy unless the need is high. Importantly, panellists reached consensus that they would prescribe an asthma biologic in pregnancy in line with criteria for people who were not pregnant, emphasising recognition of the risks of exacerbations and oral steroids in pregnancy. Additionally, many comments included the need for a careful evaluation of the risk–benefit ratio and ensuring treatment adherence and inhaler technique had been optimised before initiating biologics (appendix p 30).

More than 95% of panellists said that they would either initiate or continue an asthma biologic during breastfeeding if the patient was in agreement and the risks and benefits had been discussed. Although IgG1 is found in breast milk, transmission through this route is much lower than through placental transfer due to preferential transfer of IgG3 and IgG4 in breast milk. The concentrations of omalizumab in breast milk were 0·15% that found in maternal serum, and less than 0·5% that of maternal serum for mepolizumab and 5–7% that of maternal serum for reslizumab.[22] Insufficient information exists for the other asthma biologics. Additionally, their large molecular size and proteolytic degradation suggest that oral bioavailability in the infant is likely to be low.[30] However, the potential effects of local and systemic exposure in the infant are unknown, and this uncertainty should be discussed with patients.

An area in which consensus was not achieved was advice regarding live-attenuated infant vaccination schedules. Guidelines from the American Gastroenterological Association and the British Society of Rheumatology advise avoiding live vaccinations for the infant for the first 6 months of life if the mother received biologic therapy during the third trimester.[29,35] Many panellists commented on their inexperience and the paucity of evidence (from clinical trials, registries, and real-world studies) in this area and questioned whether the respiratory team are best placed to provide this advice. These comments emphasise the need for multidisciplinary approach, including both obstetrics and paediatric teams. Whether a consensus was reached was associated with the level of experience with the biologic, with newer biologics (eg, tezepelumab) generating the lowest levels of consensus.

A key theme throughout the Delphi study was the need for shared decision making with patients. Statements that initially included a component relating to discussions on the risks and benefits and patient agreement, or had these components added, achieved consensus. Data collected on why panellists were hesitant to prescribe asthma biologics in pregnancy (appendix p 19) show that the majority of participants felt there was a lack of real-world safety data, a lack of national or international guidelines, and concerns about potential harm, highlighting the importance and need for shared decision making in this area. Pfaller et al provide a prototypic example of how to deliver informed and shared decision making when managing biologics in women of reproductive age.[32] The development of an internationally available patient information sheet might serve to support physicians in this area by providing unified information to pregnant patients with severe asthma, promoting informed decision making. The steering committee are working to develop such an aid.

It is well known that better asthma control during pregnancy is associated with lower rates of maternal and fetal adverse events. For many people with severe asthma, biologic treatments are needed to improve asthma control and reduce oral steroid use, which has many well documented adverse effects during pregnancy that can be minimised with the use of biologics. The benefits of biologics need to be balanced against the uncertainty regarding their safety during pregnancy, which is largely due to the scarcity of randomised controlled trials and observational studies with long-term follow up of pregnant people who have used biologics during pregnancy and their offspring. Initial safety data from post-marketing surveillance studies are beginning to emerge. Since 2021, there have been 36 reports of adverse drug reactions related to dupilumab used for atopic dermatitis in pregnancy, the puerperium period, and the perinatal period, none of which were associated with dupilumab.[19] Similarly, the EXPECT registry observed a 4·4% prevalence of major congenital anomalies in women using omalizumab during pregnancy, which is consistent with levels reported for that of both people with asthma and the general population.[21] Data from post-marketing

surveillance studies on mepolizumab, benralizumab, and dupilumab are yet to be released and not expected for a few years (NCT04173442, NCT04287621).[23]

The limitations of Delphi methodology should be acknowledged. Statements are subject to interpretation and are one-sided, which might bias panellists. In part, this bias is countered by the anonymous nature of the Delphi, which encourages honest responses, and the opportunity for comments throughout the survey allowed panellists to feedback concerns on statement wording or ambiguity.[36] Although Delphi methodology provides a consensus expert opinion, it is not a substitute for randomised controlled trials or large observational cohorts to inform on drug safety during pregnancy and generate data to inform international guidelines. However, regarding our aim to support clinicians in the care of pregnant people with asthma, this Delphi generates some feedback based on collective intelligence for clinicians in an area where higher quality evidence is unavailable. Additionally, the threshold for achieving consensus was set before data collection.[36]

This Delphi study had a notable international presence, with representatives from 32 countries participating and a low panellist attrition rate between rounds (23 [16·3%] of 141). However, some countries were under-represented, which might have influenced the responses, given the differing criteria for biologic eligibility and level of pharmacovigilance in many countries.[34] Alternatively, the UK was over-represented with 62 (44%) of 141 panellists currently working in the UK, reflecting the steering committee being largely UK-based. However, we attempted to include as many countries as possible, with Delphi participation invitations being widely circulated through the International Severe Asthma Registry and the Severe Heterogeneous Asthma Research Collaboration, Patient-centred.

In conclusion, the increasing use of asthma biologics, reflecting their steroid-sparing ability alongside heightened clinician and patient concern regarding steroid-related harm, has produced substantial uncertainty about their use in pregnancy. This international Delphi study has generated a set of consensus themes that highlight the importance of risk versus benefit discussions with patients and support shared clinical decision making, with overall consensus from panellists in this study that asthma biologics can be used during conception, initiated during pregnancy in line with prescribing criteria in non-pregnant patients, continued throughout pregnancy, and used during breastfeeding. As is usual practice in people who are not pregnant, during pregnancy, asthma biologics should be reserved for people whose asthma is uncontrolled despite optimising treatment of their comorbidities, inhaler technique, and treatment adherence.

Contributors

JN and HR were responsible for study conceptualisation, project administration, and survey conduct. JN, DJJ, MC, GdA, LGH, PD, AB, and HR formed the core steering panel and were responsible for methods, investigation, study supervision, data curation, formal analysis, writing of the original draft, and reviewing and editing of the manuscript. JN and HR accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JN and MC declare no competing interests. DJJ has received advisory board and speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Sanofi and research grant funding to his institution from AstraZeneca. GdA has received grants from AstraZeneca, GSK, and Chiesi; consulting fees and payment for educational events from AstraZeneca, GSK, Sanofi, and Chiesi; and support to attend meetings from Chiesi and Sanofi. LGH has received research grant funding to his institution from GSK, AstraZeneca, and Roche/Genentech; lectures fees from AstraZeneca, Novartis, Roche, Genentech, Sanofi, Circassia, GSK, Chiesi, and Teva; and travel funding from AstraZeneca and GSK. LGH has sat on Novartis, Roche/Genentech, GSK, Teva, and Celltrion monitoring and advisory boards. PD has received advisory board fees, speaker fees, and congress travel support from AstraZeneca, GSK, Chiesi, and Sanofi. AB has received research grant funding to his institution from AstraZeneca and lecture fees from Chiesi. HR has received advisory board and speaker fees from GSK, Chiesi, AstraZeneca, Sanofi, and Boehringer Ingelheim; conference support from AstraZeneca; and grant funding to her institution from AstraZeneca and GSK.

Data sharing

A summary of deidentified participant responses are available in the appendix of this manuscript. No other study data including individual participant responses will be available for access. Further details can be sought via email to the corresponding author.

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